Neurotoxicity Research, 2003, Vol. 5 (1-2). pp.1-26

F.P. Graham
F.P. Graham Publishing Co.

Brain Sites of Movement Disorder: Genetic and Environmental Agents in Neurodevelopmental Perturbations

T. PALOMO[a], R.J. BENINGER[b], R.M. KOSTRZEWA[c] and T. ARCHER[d*]

[a]*Servicio de Psiquiatria, Hospital 12 de Octobre, Ctra. Andalucia Km. 5,400, 28041 Madrid, Spain;* [b]*Departments of Psychology and Psychiatry, Queen's University, Kingston, Canada K7L 3N6;* [c]*Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614-1708, USA;* [d]*Department of Psychology, University of Göteborg, Box 500, SE-40530 Göteborg, Sweden. trevor.archer@psy.gu.se*

(Received 15 May 2002; Revised 25 June 2002; In final form 30 June 2002)

In assessing and assimilating the neurodevelopmental basis of the so-called movement disorders it is probably useful to establish certain concepts that will modulate both the variation and selection of affliction, mechanisms-processes and diversity of disease states. Both genetic, developmental and degenerative aberrations are to be encompassed within such an approach, as well as all deviations from the necessary components of behaviour that are generally understood to incorporate "normal" functioning. In the present treatise, both conditions of hyperactivity/hypoactivity, akinesia and bradykinesia together with a constellation of other symptoms and syndromes are considered in conjunction with the neuropharmacological and brain morphological alterations that may or may not accompany them, e.g. following neonatal denervation. As a case in point, the neuroanatomical and neurochemical points of interaction in Attention Deficit and Hyperactivity disorder (ADHD) are examined with reference to both the perinatal metallic and organic environment and genetic backgrounds. The role of apoptosis, as opposed to necrosis, in cell death during brain development necessitates careful considerations of the current explosion of evidence for brain nerve growth factors, neurotrophins and cytokines, and the processes regulating their appearance, release and fate. Some of these processes may possess putative inherited characteristics, like a-synuclein, others may to greater or lesser extents be endogenous or semi-endogenous (in food), like the tetrahydroisoquinolines, others exogenous until inhaled or injested through environmental accident, like heavy metals, e.g. mercury. Another central concept of neurodevelopment is cellular plasticity, thereby underlining the essential involvement of glutamate systems and *N*-methyl-D-aspartate receptor configurations. Finally, an essential assimilation of brain development in disease must delineate the relative merits of inherited as opposed to environmental risks not only for the commonly-regarded movement disorders, like Parkinson's disease, Huntington's disease and epilepsy, but also for afflictions bearing strong elements of psychosocial tragedy, like ADHD, autism and Savantism.

Keywords: Cerebellum; Basal ganglia; Limbic; Striatum; Glutamate; Heavy metals; Iron overload; Tetrahydroisoquinolines; Apoptosis; Necrosis; Neurotoxins; Neurotrophins; Dopamine; Motor activity

INTRODUCTION

Although the neurodevelopmental background to movement disorders may be expected generally to cover environmental and genetic accidents underlying the so-called neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease, motor neuron disease, epilepsy, etc., one may make a case too for several other disease states that make their debut during childhood years, for example autism, Aspberger's syndrome, Tourette's syndrome and Lesch-Nyhan syndrome to be considered among the movement disorders, at least on the basis of diagnostic overlap (cf. Szatmari *et al.*, 1989). Thus, for example, the role of functional deficits in clinical case studies of autistic and/or savant children is described by De Long *et al.* (2003). Similarly, Attention Deficit Disorder with Hyperactivity (ADHD) may be considered too from the perspective of a movement disorder with undoubted signs and symptoms of a psychiatric cluster of functional disturbances. Typically ADHD children display a broad spectrum of clinical signs including not only the direct disorders of movement, such as hyperactivity, eye movement disorder, orienting defects and co-ordination problems but also inattention, impulsivity, learning disabilities, conduct disorders, etc., that taken together may be summarized as defects of emotional, attentional and motor co-ordination subserved by the cerebellum (Schmahmann, 1999a,b). It is interesting to note then that current models of ADHD focus not merely upon hyperactivity, attentional deficits and other

*Corresponding author: Tel: +48-126623232; Fax: +48-126374500; Email: trevor.archer@psy.gu.se
ISSN 1029 8428 print/ ISSN 1476-3524 online

motor signs, e.g. oculomotor abnormalities (Mostofsky *et al.*, 2001) and neuromotor dysfunction (Schuerholz *et al.*, 1997; 1998), but ever more upon the role of executive functioning, working memory and behavioural inhibition (Denckla, 1993; 1996; Barkley, 1997; 1998). In this vein, the putative role of the 5-hydroxytryptamine-transporter in austistic spectrum disorders, reviewed in conjunction with the situation of the "idiot savant", or unusual intellectual achievement syndrome, does bear consideration (DeLong *et al.*, 2003). This 'broadened' approach bears with it the clear implications of "neurodevelopmental" disturbances of several anatomical sites including the frontal cortex, hippocampus, basal ganglia (Aylward *et al.*, 1996), corpus callosum (Baumgardner *et al.*, 1996) and, not least, the cerebellum. Indeed, it is intriguing that the cognitive and emotional changes may be the primary clinical manifestations of cerebellar dysfunction.

ROLE OF CEREBELLUM - CEREBRUM INTERACTIONS IN HYPERACTIVITY DISORDER

A terminology has been coined that implicates the cerebellum and pertains to many of the functional deficits characteristic of ADHD, which includes "dysmetria of thought" (Schmahmann, 1991; 1998; 1999a,b) or "cognitive dysmetria" (Arndt *et al.*, 1998). There are several lines of evidence that focus upon the role of the cerebellum in the adequate functioning of the brain: Phylogenetic evidence suggests that the increase in size of the cerebellar hemispheres, during the recent million years, has paralleled the dramatic evolutionary increase in the size of the frontal lobes (Altman and Bayer, 1997; Voogd and Glickstein, 1998). Furthermore, although the cerebellar cortex occupies only 10% of the total brain volume, it contains more than half of all neurons in the brain. In boys afflicted by ADHD cerebellar volume is significantly smaller (Berquin *et al.*, 1998). This decrease in cerebellar volume has been described in two studies: Castellanos *et al.* (1996) in which 57 boys aged 11.7 [range: 5.8-17.8] were compared to controls (55 boys aged 12.0 [range: 5.5-17.8]) and Mostofsky *et al.* (1998) in which 12 boys aged 11.3 [range: 8.2-14.6] were compared to controls (23 boys aged 11.3 [range: 6.6-24.6]). Riva and Giorgi (2000) found that damage to those regions of the cerebellar vermis involved in autonomic regulation, eye movement and control/regulation of *midbrain cell body regions* caused attentional defects and emotional imbalance in children. In the laboratory (Altman and Bayer, 1997), it was shown that X-ray exposure induced lesions from postnatal day (PD) 4 - PD 15 or others exposed during PD 12 - PD 15 that devastated late dividing cell populations as compared to agenesis of the posterior inferior lobes VIII-IX, an example of experimentally induced accelerated apoptosis, caused severe motor defects. In the former case (PD 4 - PD 15), an hypoactivity in spontaneous wheel running as measured by revolutions per day (39% of controls) was observed whereas in the latter case (PD 12 - PD 15) an hyperactivity of wheel running behaviour was obtained (243 % of controls). A recessive mutation in mice that causes otoconia agenesis in the vestibular organs (Douglas *et al.*, 1979), which project to the posterior inferior vermis via the lateral vestibular nucleus (Xiong and Matsushita, 2000), also induces hyperkinesias.

Anatomical, electrophysiological, neurochemical and biobehavioural evidence points to the influences of the deep cerebellar nuclei upon midbrain projections to the nucleus caudatus, nucleus accumbens, amygdala complex and hypothalamus, all regions intimately involved in various aspects of motor, cognitive and emotional behaviour (cf. Snider and Maiti, 1976; Snider *et al.*, 1976; Tellerman *et al.*, 1979; Snider and Snider, 1982; Haines *et al.*, 1997). Using push-pull cannulae, Nieoullon *et al.* (1978) found that electrical stimulation of the right cerebellar dentate nucleus elicited long-lasting increases in [^{3}H]dopamine ([^{3}H]DA) release from the left caudate nucleus whereas a decrease was obtained in the opposite caudate nucleus. These increases/decreases in the caudate were associated with an opposite pattern of [^{3}H]DA release from the corresponding substantia nigra. Electrical stimulation of the right fastigial nucleus caused increased release of [^{3}H]DA from the ipsilateral caudate and decreased release of [^{3}H] DA from the ipsilateral substantia nigra. Other cerebellar vermal-DA interactions were demonstrated in a range of studies (Nieoullon *et al.*, 1978; Dempesy *et al.*, 1984; Albert *et al.*, 1985; Klitenick *et al.*, 1995; Volkow, 1997). Regarding otoconia agenesis, mice with this disturbance (see above) display a similar hyperactivity to that shown by DA transporter (DAT) knockout mice (Giros *et al.*, 1996; Gainetdinov, 1999), with behavioural normalisation (activity reduction) by psychostimulant administration. Disturbances in the DAT, as expressed by increased density of DAT in the striatum, are quite well established in the hyperactivity disorder (Dougherty *et al.*, 1999; Krause *et al.*, 2000). The psychostimulant, methylphenidate, affects both DA systems in the basal ganglia, through DAT, as well as in the cerebellar vermis. There is lobular and laminar specific DA innervation of primate posterior inferior vermis which is rich in axons immunoreactive for DAT (Melchitzky and Lewis, 2000). Taken together, these divergent lines of evidence may allow a convergent working hypothesis: an intrinsic imbalance cerebellar and

basal ganglia effector systems in the expression of motor disorders (Stein and Aziz, 1999). Finally, the presence of both tyrosine hydroxylase- and dopamine-beta-hydroxylase-positive neurons and fibres in the developing human cerebellum (Yew *et al.*, 1995), with expected possibilities for disturbances in the catecholamine systems concerned, as demonstrated by numerous laboratory studies (Archer *et al.*, 1988; Archer and Fredriksson, 1992; Kostrzewa *et al.*, 1994; King *et al.* 2000) provides further evidence for an interactive role of the cerebellum and DA pathways in the control of locomotion.

PRESENCE OF MERCURY IN NEURODEVELOPMENT

The implications of mercury-containing compounds in biobehavioural disturbances following perinatal exposure have received some degree of documentation (Fredriksson *et al.*, 1992; 1993) although, for example, some sources indicate that abnormalities in the nervous system have been demonstrated only for prenatal, and not postnatal, exposure to low doses of methylmercury (Danielsson *et al.*, 1993). Nevertheless, the detrimental effects of methyl mercury upon the developing brain and CNS are well-documented (Chang *et al.*, 1977a,b; Shimai and Satoh, 1985; Vorhees, 1985; Stoltberg-Didinger and Markwort, 1990). The dilemma of causality (Frankish, 2001) in the eventual role of these compounds in disrupting neurodevelopment has been highlighted recently with the case of thimerosal (Pless and Risher, 2000), a mercury-containing compound used as a preservative in some vaccines, that may or may not place children at risk for neurologic developmental disorders that include autism, ADHD and movement disturbance. Thimerosal, utilised since the 1930s to prevent bacterial contamination in multidose vaccine preparations, is metabolised to ethylmercury, closely related to methylmercury. Moderate-to-high doses are known to possess some neurotoxic action and certainly to induce neurobehavioural and/or structural deficits, even at lower doses (Tagamets and Horwitz, 1999; Redwood *et al.*, 2001; Bigham *et al.*, 2002). For example, the neonatal exposure of rat pups to metallic mercury during PD 11-PD 17, 'the period of brain growth spurt' (Davison and Dobbing, 1968) led to a number of behavioural alterations in these animals when tested as adults:

There was a dose-dependent concentration of mercury in the dissected-out organs of animals sacrificed one week following exposure to Hg^o.

Rats that had been exposed to the high dose of Hg^o showed a marked increase in locomotor and total activity but a decrease in rearing behaviour when tested at 2-months-of-age. During testing at 4-months-of-age these rats demonstrated marked hypoactivty over all three parameters. Rats that had received the low dose showed no behavioural alterations at 2-months-of-age but at 4-months the same pattern, including increased locomotion and total activity accompanied by reduced rearing, that was evidenced by the high dose group at 2-months.

Spatial learning ability assessed in the radial arm maze indicated dose-related deficits in the Hg^o-exposed offspring.

Spatial navigation measured in a circular water maze showed no evidence of any deficits due to neonatal Hg^o treatment (cf. Fredriksson *et al.*, 1992).

The purpose of describing these results, now a decade past, is to imply that the processes of cellular destruction, set in motion during the period of critical brain development, and expressed in terms of functional disturbance, tend to continue throughout the life process and, arguably, may serve to hasten the later onset of the aging process. In the light of these changes, note (a) as a result of longterm treatment the noradrenaline of the cerebellum only was affected and (b) the neurotrophin constitution (elevated hippocampal NGF, reduced septal NGF) was altered by exposure of the developing brain to methylmercury (Lärkfors *et al.*, 1991; Lindström *et al.*, 1991).

SPONTANEOUS HYPERTENSIVENESS IN HYPERACTIVE STATES

In considerations of neurodevelopment bases of hyperactivity as disorders of movement (cf. Taylor, 1998) some attention ought to be given to the particular profiles of Spontaneously Hypertensive Rats (SHR) that have been studied quite comprehensively (cf. Okamoto and Aoki, 1963). Pertinent to present purposes, SHRs display certain functional similarities to rat models (generally denervation-induced) of ADHD, most particularly an ongoing level of spontaneous hyperactivity (e.g. Knardahl and Sagvolden, 1979; Myers *et al.*, 1982; Cierpial *et al.*, 1989; Wultz *et al.*, 1990; Sagvolden *et al.*, 1992; 1993). Furthermore, as with the ADHD condition, SHRs are afflicted by DA-system abnormalities, such as irregularities in DA release (Tsuda *et al.*, 1991; Russell *et al.*, 1995) and elevations of the DAT density (Watanabe *et al.*, 1997). Thirdly, the hyperactive condition, which generally covers both locomotor and rearing behaviour, is found invariably to be ameliorated by administrations of low doses of psychostimulants, e.g., D-amphetamine or methylphenidate (Myers *et al.*, 1982; Wultz *et al.*, 1990), as in the ADHD case (Sykes *et al.*, 1971; Shatwitz *et al.*, 1976 1978; Pappas *et al.*, 1980; Luthman *et al.*, 1989;

TABLE I Spontaneous motor activity habituation quotients by (i) neonatal 6-OHDA-treated and vehicle-treated rats, (II) WKY and SHRSP strains of rats, and (III) MK-801-treated and vehicle-treated mice. (I) 6-OHDA, dissolved in 0.9% physiological saline containing 0.1% ascorbic acid (vehicle) was administered intracisternally on postnatal days 1 or 2 to groups of rat pups at a dose (free base) of 100 μg (6-OHDA 100 μg group) in a volume of 10 μl, whereas the control groups [Vehicle] were administered an equal volume of the vehicle solution alone, 30 min after systemic injections of the DA re-uptake inhibitor, GBR 12909. (II) Juvenile male-SHRSP and control age-matched male-Wistar-Kyoto (WKY) rats derived at the laboratory of Ueno *et al.* (2002), [data extrapolated from their Figure 1]. (III) Male mouse pups were administered MK-801 (0.5 mg/kg), or Vehicle (0.9% physiological saline), s.c. on postnatal day 11, at 08.00, 16.00 and 24.00 h (a total of three injections).

	Habituation Quotient, Q^1		*Habituation Quotient, Q^2*	
	Ambulation	**Rearing**	**Ambulation**	**Rearing**
Sal-Veh	163 ± 18	223 ± 15	1296 ± 87	1858 ± 275
Sal-6-OHDA	73 ± 11	76 ± 8	126 ± 54	79 ± 41
GBR-VEH	188 ± 27	201 ± 31	988 ± 122	2012 ± 336
GBR-6-OHDA	179 ± 24	205 ± 34	1047 ± 163	1741 ± 197
	Horizontal	Vertical	Horizontal	Vertical
WKY*	448	757	389	350
SHRSP*	188	220	184	168
	Locomotion	Rearing	Locomotion	Rearing
Vehicle	234 ± 24	259 ± 63	2142 ± 257	9129 ± 239
MK-801	49± 9	41 ± 7	106 ± 23	269 ± 70

* Assessed quotients from estimation of published material, Ueno *et al.*, 2002.

Archer and Fredriksson, 1992; Seeman and Madras, 1998). Nevertheless, despite the utility of the SHR model, there are several reasons to consider too a different strain, the stroke-prone SHR (SHRSP) rat strain, that was derived from certain SHR sub-strains some time ago (Okamoto *et al.*, 1974). It appears that the SHRSPs display even higher levels of motor activity and greater aggressive behaviour than the SHRs (Togashi *et al.*, 1982; Minami *et al.*, 1985). Interestingly, SHRSPs exhibit disturbances of serotonergic neurochemistry (Togashi *et al.*, 1994), which is well-documented in hyperactive DA-depleted rats (Heffner and Seiden, 1982; Snyder *et al.*, 1986; Luthman *et al.*, 1987; Jackson and Abercrombie, 1992; Radja *et al.*, 1993) and in some ADHD patients (Saul and Ashby, 1986; Spivak *et al.*, 1999), but not SHRs. Another index of similarity, albeit circumstantial, involves the disrupted brain regional blood and/or hypofrontality in ADHD patients (Rubia *et al.*, 1999; Gustafsson *et al.*, 2000) and SHRSPs (Yamori and Horie, 1977). Thus, SHRSP rats provide a useful animal model for several aspects of ADHD, not least through associations of the disorder with orbitalfrontal lobe epilepsy (Powell *et al.*, 1997).

Movements disorders initiated during early life may be expressed in behavioural indices other than direct measures of spontaneous motor behaviour. For example, rodents placed in motor activity test situations, whether this be an open-field, holeboard or an automatically-recording, photocell equipped test chamber, will under normal conditions show a decrease in the parameters of activity over time (generally counted in minutes). Usually, this decrement is considered to indicate an habituation in response to increasing familiarity to the previously novel properties of the test situation. Habituation is a relatively simple, nonassociative form of learning in situations where repeated measures of behaviour are monitored. Disruption of habituation following both perinatal and adult animal interventions has been increasingly demonstrated (Fredriksson *et al.*, 1999; 2000; 2001; 2003; Archer and Fredriksson, 2001; Fredriksson and Archer, 2002; 2003). Within the context of ADHD considerations, habituation disturbance offers an interesting state that relates aspects of movement with attentional and/or working memory changes (Casey *et al.*, 1997; Rubia *et al.*, 1999; Schweitzer *et al.*, 2000), with particular reference to neuroanatomical sites suspected to be involved, e.g. frontal cortex, basal ganglia, hippocampus and cerebellum (Teicher *et al.*, 1996; 2000).

Surprisingly, there appears to exist a remarkable consistency between at least three different, currently relevant animal models of ADHD, each incorporating a critical movement disorder component, namely the neonatal intraventricular 6-hydroxydopamine (6-OHDA) DA-depletion model (cf. Archer *et al.*, 2003), the SHRSP

TABLE II Drug effect quotients for locomotor and rearing behaviour by (I) 6-OHDA treatment: Sal-Veh, GBR-Veh, Sal-OHDA and GBR-OHDA groups, (II) WKY and SHRSP strains of rats, derived at the laboratory of K.Ueno *et al.* (2002), [data extrapolated from their Figure 1], and (III) MK-801-treated and vehicle-treated mice. For details of treatment, see Table 1. Each adult rat was placed in the motor activity test chamber for 60 min following which it was removed, injected D-amphetamine/saline and then replaced in the same test chamber. Post-amphetamine/saline locomotion and rearing counts were used for the analysis.

	Locomotion		**Rearing**	
D-amphetamine	**Saline**	**0.25**	**Saline**	**0.25**
Sal-Veh	298 ± 42	51 ± 7.5	194 ± 32	32 ± 5.1
Sal-6-OHDA	102 ± 14^{A}	199 ± 13^{B}	221 ± 57	206 ± 1^{B}
GBR-VEH	275 ± 79	52 ± 6.7	232 ± 48	39 ± 6
GBR-6-OHDA	289 ± 49	54 ± 5.4	190 ± 52	29 ± 7
	Horizontal		**Vertical**	
Methylphenidate	Vehicle	0.10	Vehicle	0.10
WKY	1336		1917	
SHRSP	168	322	155	315
	Locomotion		**Rearing**	
D-amphetamine				
Vehicle	576 ± 257	87 ± 12	716 ± 301	90 ± 32
MK-801	102 ± 15^{A}	319 ± 72^{A,B}	106 ± 19^{A}	5554 ± 193^{A,B}

Values represent mean Drug effects quotients ± SD of n = 8 or 6 rats, or 8 mice; $^{A}p < 0.01$, versus Sal-Veh or Vehicle, $^{B}p < 0.01$, vs saline, Tukey HSD-tests.

model (Ueno *et al.*, 2000; 2002) and the postnatal N-methyl-D-aspartate (NMDA) antagonist treatment model, see below (Fredriksson *et al.*, 2003). Here, a comparison is presented between assessments of habituation in each case. In order to access the extent of habituation to the activity test chambers from the DA-depletion model (Archer *et al.*, 2003a) over each successive 20-min interval, an habituation quotient for each rat was derived by dividing the numbers during the 1st 12-min by that obtained during the 2nd 12-min period, and counts during the 2nd 12-min period by those obtained during the 3rd 20-min period. In order to access the extent of habituation to the activity test chambers from the the postnatal NMDA antagonist treatment model (Fredriksson *et al.*, 2003) over each successive 20-min interval, an habituation quotient for each rat was derived by dividing the numbers during the 1st 20-min by that obtained during the 2nd 20-min period, and counts during the 2nd 20-min period by those obtained during the 3rd 20-min period. Finally, In order to access the extent of habituation to the open-field test environment from the SHRSP model (Ueno *et al.*, 2002) over each successive 20-min interval, an habituation quotient for each rat was derived by dividing the numbers during the 1st 12-min by that obtained during the 2nd 12-min period, and counts during the 2nd 12-min period by those obtained during the 3rd 20-min period. In each case the result of each division was multiplied by 100 to provide a quotient, i.e. Q_1 and Q_2, representing the reduction of activity counts from the first to the second to the third period for each mouse (cf. Fredriksson *et al.*, 1992; 1996; Danielsson *et al.*, 1993). Thus, the obtained quotients were subjected to split-plot ANOVA that indicated significant Groups x Quotients interactions, as shown below (Table 1). The markedly lower habituation quotients of the 'hyperactivity' conditions, i.e. Sal-OHDA, SHRSP or dizocilpine (MK-801), are associated with different 'accidents' assumed to underly each case, i.e. postnatal neurotoxin, genetic manipulation or an antiglutamatergic intervention affecting developmental plasticity. Note that the basal hyperactivity of each condition is complicated in each case by the failure to learn about the novelty status of the situation, a failure to habituate.

In order to access the effects of drug/saline treatment over the course of the whole 60-min test period in the activity test chambers over each successive 12-min (or 30-min[SHRSP] or 20-min[MK-801]) interval, a 'Drug-effect' (DE) quotient for each rat was derived by dividing the numbers of counts (locomotion and rearing, respectively) during the 1st 12-min by that obtained during the

TABLE III Effects of neonatal administration of MK-801 upon spontaneous motor behaviour of mice tested at adult age. Mean locomotion, rearing and total activity counts over successive 30-min test periods. Newborn male mouse pups were injected either MK-801 (0.5 mg/kg, s.c.) or vehicle (0.9% saline) on postnatal day 11 at three different times (0800, 1600 and 2400 h).

	N	Locomotion		Rearing		Total Activity	
Vehicle	20	906±70	27±4	2410±108	16±8	10023±613	2712±77
MK-801	20	283±91*	639±118*	1043±133*	649±121*	4612±593*	6073±703*
(%)		(31)	(2367)	(43)	(4056)	(46)	(224)

Values represent means±SD; (%) = percent of vehicle control value; *$p < 0.01$, versus vehicle, Tukey HSD-testing.

2nd 12-min (or 30-min[SHRSP] or 20-min[MK-801]) period, thereby providing a DE quotient for the 1st to 2nd 12-min test period following D-amphetamine/saline/methylphenidate injections to the neonatal treatment/hypertensive groups. In each case the result of each division was multiplied by 100 to provide a quotient representing the reduction/increase of activity counts from the 1st to the 2nd period for each rat/mouse/group of rats [SHRSP] (cf. Fredriksson *et al.*, 1992, 1999; Archer and Fredriksson, 2000).

Table II depicts the activity-reducing effects (as assessed by DE Quotients) of low doses of psychostimulant compounds, D-amphetamine at 0.25 mg/kg and methylphenidate at 0.10 mg/kg, upon hyperactive Sal-6-OHDA rats, SHRSP rats or MK-801 mice from the 1st 12-min, 30-min or 20-min period to the 2nd period. Thus, it will be noted that D-amphetamine generally increased locomotion and rearing (values less than 100) in all the control groups whereas D-amphetamine/methylphenidate reduced motor activity levels of the hyperactive Sal-6-OHDA rats, SHRSP rats and MK-801 mice.

NMDA DISTRUBANCES UNDERLYING APOPTOSIS

During the development of the brain and through cell multiplication, induction, migration, proliferation and differentiation, there occurs an initially high, but tapering, period of cell death (Hamberger and Openheim, 1982), much of which may be apoptotic or naturally-occurring pre-programmed cell death (Wilkie *et al.*, 1980). As a consequence the developing brain is highly susceptible to disturbances of both neuronal survival and alignment (Sarnat, 1987). The end-product of these developmental cascades will be the topographic and morphologic integrity of specific and physiologically functional neurons in discrete circuits and neural networks (Sastry and Rao, 2000). Several different factors modulate the eventual survival of the developing neurons, including the interaction between neurotrophic compounds (Levi-Montalcini, 1966) and activity at NMDA receptors (Connor and Dragunow, 1998). Several recent lines of investigation have demonstrated that NMDA antagonists potentiate apoptosis in neonatal rats (e.g. Olney *et al.*, 1991, 2000; Ikonomidou *et al.*, 1999, 2000). In order to study the apoptosis-accelerating properties of these compounds, the effects of postnatal MK-801 administration were studied, as follows: male mouse pups were injected with either MK-801 (0.5 mg/kg, s.c.) or vehicle (0.9% physiological saline) on PD 11 at three different times (0800, 1600 and 2400 hours), and then returned to their mothers until weaning at PD 25. On PD 12, a few MK-801-treated and vehicle-treated mice were sacrificed and mouse brain sectios were analysed using fluoro-Jade analysis, according to the procedure outlined previously (Schmued *et al.* 1997; Schmued and Hopkins, 2000). On PD 71, MK-801 and vehicle mice were tested for spontaneous motor activity, as described previously (Archer *et al.*, 1986). Thus, each mouse was placed in an ADEA test chamber and motor activity was registered over 2 x 30 min test periods. Table III presents the spontaneous motor activity of the MK-801 and vehicle treated mice over successive 30-min test periods. Postnatal MK-801-treated mice showed a marked hypoactivity during the 1st 30-min test period: percent of control values were less 50% for locomotion, rearing and total activity, and a marked hyperactivity during the 2nd 30-min test period: percent of control values were 2367%, 4056% and 224% for each of the three activity parameters, respectively.

Further testing of the MK-801-treated mice following acute treatment with a low dose of D-amphetamine (0.25 mg/kg, s.c.) or saline indicated that the low dose of the psychostimulant, while itself inducing hyperactivity in vehicle mice, abolished the hyperactivity of the MK-801 animal (Fredriksson and Archer, 2002a). Postnatal MK-801-treated mice even demonstrated serious deficits of radial arm maze acquisition, and the acute administration of D-amphetamine (0.25 mg/kg) again abolished these deficits (manuscript in preparation). In the circular swim maze, no deficits in escape latency acquisition were evidenced until the position of the submerged platform was

TABLE IV Locomotion quotient values expressed as counts during the initial 20-min period of testing divided by total iron in the frontal cortex and basal ganglia (μg/g wet weight) of 4-month-old NMRI mice (Fredriksson *et al.*, 1999; Fredriksson *et al.*, 2000) and 4-month-old C57 Bl/6 mice (Fredriksson *et al.*, 2001; Fredriksson and Archer, 2002) and in the substantia nigra of 6-month-old Wistar rats (Schröder *et al.*, 2001) following oral exposure to iron (Fe^{2+}) on postnatal days 10-12, at the various doses specified below. Comparison of the locomotion quotient values over these brain regions in the different iron overload studies applying comparable conditions of iron administration postnatally.

	Fredriksson et al. (1999)		**Fredriksson et al. (2000)**		**Fredriksson et al. (2001)**		**Fredriksson & Archer (2002, 2003)**		**Schröder et al.(2001)**
Doses Fe^{2+}	**Front.C.**	**Basal G.**	**Front.C.**	**Basal G.**	**Front.C.**	**Basal G.**	**Front.C.**	**Basal G.**	**Subst.N.**
							Experiment I		Wistar rats
Vehicle	24.0	16.5	24.2	16.7	21.5	15.3	23.8	15.6	6.30*
(%)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)
2.5 mg/kg							19.1	10.2	4.02*
(%)							(80)	(65)	(64)
5.0 mg/kg							7.6	3.5	
(%)							(32)	(22)	
7.5 mg/kg							6.1	3.05	
(%)							(25)	(19)	
							Experiment II		
Vehicle							21.4	15.1	
(%)							(100)	(100)	
7.5 mg/kg							6.7	2.9	
(%)							(31)	(19)	
3.7 mg/kg	18.7	11.2							
(%)	(78)	(67)							
7.5 mg/kg			8.8	4.3	8.4	3.6			3.47*
(%)			(36)	(25)	(39)	(23)			(55)
15.0 mg/kg									3.28*
(%)									(52)
30.0 mg/kg									2.31*
(%)									(37)
37.0 mg/kg	6.7	3.2							
(%)	(28)	(19)							

Iron content was analysed as μg/g wet weight of tissue in each of the studies referred above. Locomotion quotient values are derived from the mean locomotion counts of each iron dose group, or vehicle group, indicated divided by the mean tissue level of total iron for that group. (%) = percent of vehicle locomotion quotient value. *Open-field crossings were registered over 15-min periods. *Note:* Front. C. = Frontal Cortex; Basal G. = Basal Ganglia; Subst. N. = Substantia Nigra.

shifted: then MK-801-treated mice showed a serious retention performance deficit. Fluoro-jade staining per mm^2 regional brain tissue of MK-801 mice pups expressed as percent of vehicle mice pups showed also that the extensiveness of staining was markedly greater in the hippocampus. Percent postnatal MK-801: vehicle:- Hippocampus = 363%; Frontal cortex = 223%; Cerebellum = 210%. Thus, postnatal injections of MK-801 induced a greater rate of degenerating cell loss (apoptosis) in the three regions examined compared to vehicle injected mice. Finally, the postnatal administration of both ketamine, the NMDA antagonist, and a high dose of ethanol each induced initial hypoactivity followed by hyperactivity in the activity test chambers (Fredriksson *et al.*, unpublished data). Olney *et al.* (1989, 1991, 2000; 2002) have suggested that the exaggerated apoptosis to the developing brain induced by MK-801, or GABA-acting drugs like ethanol, may induce dramatic disruptions of function both during a child's development (e.g. in disorders like ADHD or FAS) but also an onset during early adulthood (e.g. in disorders like psychosis, substance abuse and major depression).

BRAIN TISSUE IRON ABNORMALITIES

Serious functional deficits constitute some of the abnormalities resulting from iron deficiency or iron-overload during early childhood (e.g. Yehuda and Youdim, 1989; Youdim *et al.*, 1989; Youdim and Yehuda, 2000). The putative role of iron in neurodegenerative processes leading to PD and changes in DA receptor pathways has received particular attention (Youdim *et al.*, 1983; 1993; 1999; Shoham and Youdim, 2000). Thus, the implication of brain iron in the disorder has been the focus of some considerable investigation (Ben-Shachar and Youdim, 1991; Ben-Shachar *et al.*, 1991; Gerlach *et al.*, 1994; Linert *et al.*, 1996; Gerlach *et al.*, 1997; Jellinger,

1999; Thompson *et al.*, 2001). Youdim *et al.* (2002) discuss the devastation of brain function, as assessed through different indices, wrought by abnormalities of iron metabolism in neurodegenerative disorders including PD, Huntington's disease, Alzheimer's disease (AD), Wilson's disease and Haller Vorden Spatz disease. Neuroimaging analyses, leakages of the blood-brain barrier, chronic neuroleptic treatments and inflammatory processes instigated by profilation-reactive microglia are all examined to provide an implication of the metal in the disease process. On the other hand, Gerlach *et al.* (2003) discuss the presence of neuromelanin (Double *et al.*, 1999), the granular, dark-brown pigment, as well as the deposits of iron in the degenerative processes of the pigmented DA neurons of the substantia nigra. Particularly, iron increase in basal ganglia is significant (Sofic *et al.*, 1988; Sofic *et al.*, 1991), and is detected in postmortem PD brains (Riederer *et al.*, 1989; Griffths *et al.*, 1999) and observed *in vivo* through neuroimaging (Gorell *et al.*, 1995; Rvylin *et al.*, 1995; Berg *et al.*, 2000). Thus, a situation involving the destructive interactions of iron and neuromelanin over the course of life span is described (Hirsch, 1988; Good *et al.*, 1992; Jellinger *et al.*, 1992; Offen *et al.*, 1997; 1999; Shima *et al.*, 1997; Zecca *et al.*, 2001). In a different vein, Youdim *et al.* (2002) have investigated the role of oxidative stress in the degeneration of melanin-containing DA neurons of the substantia nigra pars compacta and the neuroprotective propensities of *R*-apomorphine and 3,3-epigallocatecine-3-gallate (EGCG). They found that the selective DA neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) affected differentially the expression of prominent genes (51 out of 1200 genes from eight major functional groups. First, it was shown that MPTP increased mRNA expression of several neurotrophic factors including GDNF (Glial cell line-derived neurotrophic factor), EGF (epidermal growth factor) and VEGF (vascular endothelial growth factor), possibly reflecting compensatory sprouting of surviving neurons, and were prevented by *R*-apomorphine pretreatment. The results add further to the involvement of neurotrophic factors in parkinsonism, outlined above (see also Hadjiconstantinou *et al.* 1991; Lin *et al.*, 1993). Second, MPTP up-regulated the expression of mRNAs associated with IL 1b, IL 6, IL 7 and IL 10 and their receptors. Thus, MPTP-induced increases in cytotoxic cytokines and cytokine receptors confirmed the concept of inflammatory processes in neurodegeneration (Mogi *et al.*, 1996; Bessler *et al.*, 1999). Again, *R*-apomorphine pretreatment attenuated the MPTP-induced gene expression increase (Grunblatt *et al.*, 2001). The differentential acute effects of the DA agonists in MPTP- and neonatal 6-OHDA-induced behavioural deficits are also described (Archer *et al.*, 2002a).

Early (PD 10-12) administration of iron (Fe^{2+}) to mouse or rat pups induced marked deficits in spontaneous motor activity, habituation, and both positively and negatively reinforced instrumental learning behaviours (Archer *et al.*, 2003b; Fredriksson *et al.*, 2003). Thus, dose levels of postnatal iron administration ranging from 2.5 to 3.7 mg/kg induced deficits of spontaneous motor behaviour expressed by marked hypoactivity during the initial periods of testing (i.e. the initial 20 - 30 min) followed by a dramatic level of hyperactivity during the later stages of testing. The most critical period for administration of iron appears to be PD 10-12. Postnatal iron administration potentiates both the behavioural deficits as well as the depletions of DA and metabolites, homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC), induced by different dose levels of the selective DA neurotoxin, MPTP. The hypoactivity observed during the initial period of behavioural testing was reversed by co-administration of L-Dopa (L-dihydroxyphenylalanine) with the glutamate antagonist, MK-801, in a dose-related manner, as shown for other treatments depleting DA and inducing hypoactivity (Archer and Fredriksson, 2000). Postnatal iron overload induced also marked deficits in radial arm maze learning acquisition and retention at various different dose levels, and particularly at the critical period of administration, PD 10-12. These impairments were evidenced in both rats and mice at several different dose levels. Deficits in inhibitory conditioning and retention were obtained in the 7.5 and 15.0, but not the 2.5, mg/kg dose groups. Analyses of total iron distribution and accumulation indicated marked deposits in the basal ganglia and substantia nigra and to a much lesser extent in the frontal cortex (see Fredriksson *et al.*, 1999, 2000, 2001; Schröder *et al.*, 2001; Fredriksson and Archer, 2002). Table IV presents the locomotion quotient values expressing the mean locomotion counts during the initial 20-min (hypoactive) period of testing, but the 15-min open-field test in the Schröder *et al.* (2001) study, by vehicle and iron dose groups in each of the experiments. This analysis of locomotion quotient values indicates a remarkable degree of consistency between: (1) the vehicle groups (Frontal cortex: 24.0, 24.2, 21.5, 23.8 and 21.4; basal ganglia: 16.5, 16.7, 15.3, 15.6 and 15.1) in each of the four mouse experiments; and (2) the postnatal iron groups administered 7.5 mg/kg (Frontal cortex: 8.8, 8.4, 6.1, and 6.7; basal ganglia: 4.3, 3.6, 3.05, and 2.9). Locomotion quotient values demonstrated plausible iron dose – hypoactivity relationships as indicated by the Fredriksson *et al.* (1999) study [Panel 1], Fredriksson *et al.* (2000) study [Panel 4], and the Schröder *et al.* (2001) study in rats [Panel 5]. Finally, it will be noted that the locomotion quotient value analysis provides an exceptionally sensitive

estimation of the functional deficits of low postnatal iron doses that may be of particular interest in that assessment of the role of the frontal cortex or substantia nigra (rat study), e.g. locomotion quotient values for the 3.7 mg/kg, 2.5 mg/kg and 2.5 mg/kg (rats) groups were 7.8%, 80% and 64% (substantia nigra), respectively.

The analysis of enzymes involved in oxidative stress indicated that: (1) Formation of thiobarbituric acid reactive species (TBARS) concentration was elevated in the substantia nigra by both the 7.5 and 15.0 mg Fe^{2+}/kg doses whereas in the striatum there was a decrease. (2) Superoxide dismutase activity was decreased in a dose-related fashion in the substantia nigra but seemed elevated in the cerebellum. Iron-overload during the immediate postnatal period incorporating critical synaptogenesis seems detrimental for several aspects of functional and neurobiological development. The pattern of behavioural deficits observed in the course of these experiments has been discussed in the functional context of disorders such as PD or AD (Fredriksson and Archer, 1997; Schmidt and Kretschmer, 1997; Schmidt and Ferger, 2001). Iron-overload during the immediate postnatal period incorporating critical synaptogenesis seems detrimental for several aspects of functional and neurobiological development.

In association with this iron-based treatise of neurodeveopmental factors in PD, Riederer (2003) has examined whether or not there exists a subtype of developmental PD, in view of certain observations (Louis *et al.*, 2001). In this account, ontogenetic aspects of catecholamine systems, genetic aspects of juvenile PD, hypokinesia due to prenatal and birth-related problems, virus and disease affecting the CNS, and a chronological break-down of the major postnatal effects regulating essential catecholaminergic systems. Attention is placed upon the role of regional developmental cell death (apoptotic/necrotic) in the substantia nigra (Jackson-Lewis *et al.*, 2000) that presumably affect ontogenesis while, on the other hand, the recent evidence involving mutations in the Parkin gene (Lücking *et al.*, 2000). The possibility of an infectious disease and/or epidermic bacterial/viral source of Parkinsonism seems if not likely then at least a contributory factor to the disease pathogenesis (Masliah *et al.*, 1996; Mattock *et al.*, 1988; Itoh *et al.*, 2000; Kalita and Misra, 2000). There is ample evidence that high levels of early stress cause persistent elevations of several markers for heightened reactivity in the hypothalamic-pituitary-adrenal-axis (Levine *et al.*, 1997), with concomitant harmful outcomes for neuronal systems due to persistently high circulating levels of glucocorticoids (Levine, 2002). As discussed by Riederer (2003), the likely involvement of traumatic early stress in a form of potentiated apoptosis ought to be a feature of the neurodegenerative profile, as suggested above the role of iron, neuromelanin and ferritin at different ages may well offer an essential perspective on the stress factor (Zecca *et al.*, 2001).

STRIATAL GLUTAMATERGIC DISTURBANCE

As explained by Chase *et al.* (2003), the dominating medium-sized spiny neurons in the striatum are GABAergic cells that receive glutamatergic inputs from the cortex and project to the globus pallidus, internal segment, and the substantia nigra pars reticulata (cf. Graybiel, 2000). Structural-functional derangements of the medium spiny neurons are implicated in both instances of hypokinesia (Wirshing, 2001) or hyperkinesia (Ahlskog and Muenter, 2001; Chase and Oh, 2000). Disturbances of the striatal medium spiny neurons lead to alterations in the properties of peptide co-transmitters (Parent *et al.*, 1996), receptor configurations (Meshul and Allen, 2000), signaling molecular changes (Oh *et al.*, 1997; 1998; 1999), postsynaptic receptor density (Smith *et al.*, 1994), leading to an altered synaptic efficacy that enhances the glutamatergic input from the cortex (Calabresi *et al.*, 2000; Centonze *et al.*, 2001). Thus, it is now well-established that NMDA receptor antagonists, uncompetitive or competitive, generally in co-administration with a DA agonist or the precursor, serve to restore motor behaviour (Skuza *et al.*, 1994; Fredriksson *et al.*, 1999; 2001; Archer and Fredriksson, 2000) and/or reduce the response aberrations (Blanchet *et al.*, 1997; 1998; Metman *et al.*, 1998; Merello *et al.*, 1999; Del-Dotto *et al.*, 2001).

NEONATE DENERVATION-INDUCED DA RECEPTOR SUPERSENSITIVITY

Denervation of DA pathways in the neonate brain, using the selective catecholamine neurotoxin 6-OHDA, will cause life-long alterations to the neural configurations as a result of several ontogenetic processes, such as adaptation, neuronal reorganisation, pruning, permanent suppression of DA content in neostriatum, etc. (cf. Sachs and Jonsson, 1972; Kostrzewa and Harper, 1974; Luthman *et al.*, 1987; 1990; Kostrzewa, 1995; Kostrzewa *et al.*, 1998; 1999b). As described by Kostrzewa *et al.* (2003), there occurs in the ontogeny of the denervated neonate marked increases in serotonin in the neostriatum (e.g. Breese *et al.*, 1984), demonstrably reflecting a serotonergic hyperinnervation (e.g., Snyder *et al.*, 1986; Descarries *et al.*, 1992), that appears to be quite linearly related to the dose of neurotoxin applied and the extent of DA loss (Luthman *et al.*, 1989, 1991, 1997; Kostrzewa *et al.*,

1993) and of possible relevance to considerations of clinical syndromes (Allen and Davis, 1999; Archer *et al.*, 2002). Kostrzewa *et al.* (2003) have investigated the DA receptor supersensitivity (DARSS), following postnatal denervation, by analysing the overt supersensitivity of DA D_1 receptors and/or serotonergic to DA/serotonin agonists as expressed by vacuous chewing movements (VCMs) in several instances (Gong and Kostrzewa, 1992; Gong *et al.*, 1992; Kostrzewa *et al.*, 1993, 1999a).

It is interesting also to note, in the light of the previous mention of striatal glutamatergic disurbance, that chronic long-term treatment with haloperidol, which induces VCMs too in rats, has offered a well-documented model of tardive dyskinesia (Gunne *et al.*, 1986; Kakigi *et al.*, 1995; Tamminga *et al.*, 1990; Huang *et al.*, 1997). Long-lasting, chronic treatment with so-called typical antipsychotic compounds, such as haloperidol, is certainly neurodevelopmentally associated with a constellation of unwanted behaviours, the extrapyramidal side effects (EPSs), that generally included dystonia, akathisia, parkinsonism and tardive dyskinesia (cf. Lewander, 1994). Over and above the serotonergic connection in VCMs, it has been shown that alterations of GABAergic transmission in the substantia nigra pars reticulata are involved (Gunne *et al.*, 1984; 1988; Johnson *et al.*, 1994). Recent studies have focused upon the role of the entopeduncular nucleus and concomitant neurochemical changes in VCMs induced by both a typical, haloperidol, and an atypical, clozapine, neuroleptic (Yu *et al.*, 1999). It was shown that both haloperidol and clozapine, although with a markedly differential time-dependency, increased VCMs per unit time over 21 days of drug administration. Concurrently, glutamate decarboxylase-65 and glutamate decarboxylase-67 (not clozapine) mRNA expression in rostral and caudal regions of the entopeduncular nucleus were increased (Yu *et al.*, 1999).

ENDOGENOUS COMPOUNDS WITH NEUROTOXIC POTENTIAL

The tetrahydroisoquinolines, bearing structural similarity to the hydropyridines (of which MPTP is the best studied neurotoxin), are endogenous to the human brain (Niwa *et al.*, 1991; Zarranz de Ysern and Ordonez, 1981). Salsolinol [1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline], which has been subjected to some degree of investigation (Sandler *et al.*, 1973; Niwa *et al.*, 1987; Moser and Kömpf, 1992), is implicated in PD (Antkiewicz-Michaluk *et al.*, 1997; Naoi *et al.*, 1998a). Exogenous tetrahydroisoquinolines, present in some dairy products, wines and fruits (e.g. Deng *et al.*, 1997) may attain brain accumulation (Nagatsu, 1997; Naoi *et al.*, 1998b), thereby exerting some potential for necrotic or apoptotic cell death. Vetulani *et al.* (2003) review a series of studies examining the physiological influences of the tetrahydroisoquinolines, salsolinol and TIQ (1,2,3,4-tetrahydroisoquinoline) upon neurodegenerative processes underlying parkinsonism. The acute effects of each compound upon spontaneous motor activity (exclusively locomotor activity) are unclear: at the highest dose activity was reduced but not always significantly so. Nevertheless, the psychostimulant effects of apomorphine (0.25 mg/kg) were abolished by both TIQ (50 mg/kg) and salsolinol (100 mg/kg) whereas TIQ (5, 10, 25 or 50 mg/kg) and TIQ (5, 10, 20 or 40 mg/kg) reduced the activity-enhancing effects of amphetamine (3 mg/kg) and scopolamine (1 mg/kg), respectively. Lower doses of TIQ (5, 10 or 25 mg/kg) and TIQ (5 or 10 mg/kg) potentiated the activity-enhancing effects of morphine (10 mg/kg) and cocaine (15 mg/kg), respectively; higher doses (20 or 40 mg/kg) reduced the activity-enhancing effects of cocaine. Salsolinol at doses of 10 mg/kg and 5, 10, 20 or 40 mg/kg, respectively, induced similar effects, blocking amphetamine (3 mg/kg) and scopolamine (1 mg/kg) while potentiating morphine (10 mg/kg) at 10 mg/kg. Neurochemically it was shown that both TIQ and salsolinol displaced clonidine, the NA α_2-receptor agonist, and apomorphine, a mixed DA D_1/D_2 agonist.

Several studies by this group have demonstrated that the TIQs may exert a profound influence upon catecholamine neuropharmacology, for instance by activating DA release from striatal DA terminals (Antkiewicz-Michaluk *et al.*, 2001). Administration of TIQ elevates levels of dialysable DA in cerebral tissues (Lorenc-Koci *et al.*, 2000), which may or may not be associated with the damage inflicted upon DA systems following repeated treatment, as indicated by the reduction in levels of DA metabolites and numbers of tyrosine hydroxylase-containing terminals in rat striatum (Antkiewicz-Michaluk *et al.*, 2000; Lorenc-Koci *et al.*, 2000). Thus, there have now accumulated behavioural, neurochemical and pathological indices to implicate the TIQs in the pathogenesis of laboratory models of PD: for example in mouse brain (Kotake *et al.*, 1995; Igarashi *et al.*, 1999; Abe *et al.*, 2001a,b; Ishiwata *et al.*, 2001), rat brain (Ohta *et al.*, 1990; Ayala *et al.*, 1994; McNaught *et al.*, 1996), in the inhibition to reductions in tyrosine hydroxylase in rat brain (Scholz *et al.*, 1997), in primates, monkeys and squirrel monkeys (Yoshida *et al.*, 1993; Kotake *et al.*, 1996; Yamakawa *et al.*, 1999). Several studies in the clinic have measured levels of salsolinol, 1,2-dehydrosalsolinol, norsalsolinol, as well as free DA, DA sulphate, free salsolinol and salsolinol sulphate in Parkinsonian patients and controls (Faraj *et al.*, 1990; 1991; Dostert *et al.*,

1993; Maruyama *et al.*, 1996), and also accumulation in the human nigrostriatal pathway (Maruyama *et al.*, 1997b). Nevertheless, this elevation is not universally observed (Muller *et al.*, 1998a,b). In the lymphocytes of PD patients, the activity of the enzyme, salsolinol-*N*-methyltransferase, showed a marked increase (a factor of 5.3 times higher than that of controls) at the same time as *N*-methylsalsolinol was increased significantly in untreated PD patients (Naoi *et al.*, 1998b). Additionally, *N*-methylsalsolinol induced DNA damage and toxicicity in human dopaminergic neuroblastoma SH-SY5Y cells (Maruyama *et al.*, 1997a; Storch *et al.*, 2000).

The presence of TIQ and 1-methyl-TIQ in foodstuffs with high 2-phenethylamine was reported some time ago (Makino *et al.*, 1988). It is perhaps more important to note that both compounds pass through the blood-brain barrier easily and accumulate in tissues as endogenous or exogenous amines (Kikuchi *et al.*, 1991). This class of compounds is implicated in cell death through both necrosis and apoptosis (Maruyama *et al.*, 2000; Naoi *et al.*, 2000a,b), neurotoxicity through hydroxy radical generation (Maruyama *et al.*, 1995) and with a high degree of selectivity for dopaminergic cells (though less than 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium ion [MPP^+] via uptake by the DA transporter) (Storch *et al.*, 2002). With regard to the iron-MPTP interactions (see below), salsolinol-induced oxidative DNA damage and neuronal cell death was exacerbated by iron [of particular importance was the radical formation enhancement by Fe(II) in comparison with the lesser extent by Fe(III)] and ameliorated by the iron chelator, deferoxamine (Surh *et al.*, 2002). The isoquinolines are widely distributed in the environment and there is strong consensus that high concentration and/or prolonged exposure can lead to neurodegeneration and PD symptoms (Gerhard *et al.*, 1998; McNaught *et al.*, 1998) Nevertheless, in consideration of a possible neuroprotective action of 1-methyl-TIQ (Yamakawa *et al.*, 1999; Vetulani *et al.*, 2003), this class of compound ought to be analysed more closely from a neurodevelopmental perspective.

NERVE GROWTH FACTORS IN NEURODEVELOPMENT

The role neurotrophic factors in modulating cell death through apoptosis and necrosis during neurodevelopment has stimulated an enormous body of research into understanding brain development and function (e.g. Levi-Montalcini and Angeletti, 1968; Levi-Montalcini, 1987; Araujo *et al.*, 1990; Kerr *et al.*, 1999; Thoenen, 1995; Alexi *et al.*, 1997). The review by De Yébenes *et al.* (2003) outlines and describes the different types of nerve growth factors, i.e. neurotrophic factors and neurite-promoting factors (see also De Yébenes *et al.*, 1998). Of these, the neurotrophins, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3, -4 and –5 (NT-3, NT-4/5) and gliotrophic factors, e.g. glial cell line-derived neurotrophic factor, e.g. GDNF, have been most closely assessed with respect to functional aspects and models of brain disorders (Araujo and Hilt, 1997). Thus the influence of neurotrophins in parkinsonism has been considerable: in this regard, it was demonstrated both over a decade ago and more recently that BDNF enhanced survival of DA neurons in the substantia nigra of developing brains (Hyman *et al.*, 1991; Chun *et al.*, 2000). The role of BDNF in cellular plasticity is exemplified by the induction and maintainence of long-term potentiation (Figurov *et al.*, 1996; Korte *et al.*, 1995; Patterson *et al.*, 1996). On the other hand, GDNF modulates both the survival of midbrain DA neurons (Bowenkamp *et al.*, 1995; Gerhardt *et al.*, 1999; Chauhan *et al.*, 2001) and reduces apoptosis in foetal human dopaminergic neurons (Zawada *et al.*, 1998). Possible mechanisms of action of neurotrophins in parkinsonism (e.g. Walker *et al.*, 1998), effects upon DA neurons (Missale *et al.*, 1989), utility in primate models (Kordower *et al.*, 2000), in transgenic mice in a rodent model of Huntington's disease (Kordower *et al.*, 1997), in a PD patient (Kordower *et al.*, 1999), prevention of nigral cell loss following excitotoxic striatal-pallidal lesions (Volpe *et al.*, 1998) and neural grafting (Olson *et al.*, 1991) are described. Thus, the 'anti-degenerative' role of the neurotrophins is of much speculative interest in preserving DA neurons (Choi-Lundberg *et al.*, 1997; Levivier *et al.*, 1995). In a similar vein, Sokoloff *et al.* (2002) describe the intimate neuronal interactions between the DA D_3 receptor and BDNF in disorders influencing movement but also in behavioural sensitisation/schizophrenia. It was previously shown that the D_3 receptor was implicated in several disorders involving dopaminergic systems (Bordet *et al.*, 1997; Lammers *et al.*, 2000: Schwartz *et al.*, 2000; Sokoloff *et al.*, 2001).

Consideration of α-synuclein, a 19-kDa acidic protein at presynaptic terminals in the striatum, cerebral cortex and hippocampus (Iwai *et al.*, 1995; Hashimoto and Masliah, 1999) a major component in the Lewy bodies of PD brains, in conjunction with neurotrophic factors and cytokines, may be necessary for an understanding of the neurodevelopment of the disorder (Spillantini *et al.*, 1998; Trojanowski *et al.*, 1998; Tu *et al.*, 1998; Abeliovich *et al.*, 2000). The α-synuclein gene (PARK1) on chromosome 4q21-23 is implicated in autosomal dominant PD patients from German and Italian families (Polymeropoulos *et al.*, 1997; Krηger *et al.*, 1998; Narhi *et al.*, 1999). Furthermore, it has been found also that in

transgenic mice expressing wild-type human α-synuclein that the loss of DA terminals in the basal ganglia coincided with motor dysfunction, due to progressive accumulation of neuronal inclusions immunoreactive for α-synuclein ubiquitin (Masliah *et al.*, 2000). Recently, Satoh and Kuroda (2001) investigated the constitutive and cytokine/neurotrophin factor-regulated expression of α-synuclein in cultured human neurons [Y79 retinoblastoma, IMR-32 neuroblastoma, SK-N-SH neuroblastoma, KG-1-C glioma, HeLa cervical carcinoma, HepG2 hepatoblastoma, A549 lung carcinoma, MOLT-4 T-cell leukaemia, U-373MG astrocytoma, Ntera2 teratocarcinoma, K-562 erthroleukemia, and HL-promyelocytic leukaemia] by Northern blot and Western blot analyses. They identified the constitutive expression of α-synuclein in human neural and non-neural cell lines and that levels of α-synuclein expression were elevated markedly in Nyera2 teratocarcinoma cells following retinoic acid induced neuronal differentiation, accompanied by an increase expression of synphilin-1; α-synuclein expression levels were not affected in Ntera2-derived differentiated neurons exposed to TNF-α, ILα-1, BDNF or GDNF. It was concluded that α-synuclein in human neurons is upregulated during differentiation but unaffected by cytokine and neurotrophic factors supposedly involved in nigral cell death and survival (Satoh and Kuroda, 2001). TNF-α, IL-1β, BDNF and GDNF are potent neurotrophic factors for nigral dopaminergic neurons *in vivo* and *in vitro*, as well as being elevated in PD brains (Boka *et al.*, 1994; Mogi *et al.*, 1994a,b; Mogi and Nagatsu, 1999). Thus, alterations in glial communication (Kaul *et al.*, 2001) exert direct neuropathological effects by interfering with signals aimed at preventing apoptosis. Recent results by Bezzi *et al.* (2001) have identified a new pathway for glia-glia and glia-neuron communication relavant to normal brain functioning and escalation of neurodegeneration. Alternatively, since different avenues point towards the active role of α-synuclein during synaptogenesis (Clayton and George, 1999; Hsu *et al.*, 1998; Withers *et al.*, 1997), it is possible that synphilin-1, a constituent of Lewy bodies in PD brains (Wababayashi *et al.*, 2000), co-acting with it underpins the process of neuronal differentiation. Synphilin-1 may function to anchor α-synuclein to intracellular proteins involved in vesicle transport (Engelender *et al.*, 1999). Furthermore, Bennett *et al.* (1999) found that wild-type and Ala53Thr mutant isoforms of 6Xhis-tagged human α-synuclein fusion proteins were expressed in the human neuroblastoma cell line SH-SY5Y by transient transfections, which together with other evidence of α-synuclein aggregation in the A53T mutant (Conway et al, 1998; Giasson *et al.*, 1999), provide a possible neurodevelopmental mechanism for the expression of PD pathology.

GENETIC VERSUS ENVIRONMENTAL INFLUENCES IN PARKINSONISM

In recent years, a number of reports have investigated the genetic defects in familial Parkinsonism (e.g. Golbe *et al.*, 1996; Ishikawa and Tsuji, 1996; Morrison *et al.*, 1996; Polymeropoulos *et al.*, 1996; 1998). Interestingly, the genetic defects have been identified in some of these multigenerational kindreds (Wszolek and Markopoulou, 1999; Wszolek and Uitti, 1999). Recently, positron emission tomography, utilizing flourodopa uptake and raclopride binding, in analyses of familial parkinsonian syndrome and idiopathic parkinsonism, it was found that in assessing the similarities and differences between the disorders, more similarities than differences were existent (Pal *et al.*, 2001). Although some form of inheritance in familial parkinsonian syndrome and idiopathic parkinsonism has been suspected or even suggested (Payami *et al.*, 1995; Wooten *et al.*, 1997), the supporting evidence remains weak (Maraganore *et al.*, 1996). It is worth noting that the conclusions of twin studies do not unreservedly confirm genetic mechanisms in PD (Ward *et al.*, 1983; Marsden, 1986; Marttila *et al.*, 1988). Rather, the influence of hereditary factors appears important for early-onset PD (Pahwa *et al.*, 1993; Tanner *et al.*, 1999). Nevertheless, the predispositional effects of environmental agents ought not to be neglected (Ho *et al.*, 1989; Herzman *et al.*, 1990; 1994; Wong *et al.*, 1991;Butterfield *et al.*, 1993; Hubble *et al.*, 1993).

Although a number of studies indicate that the presence of Parkinsonism in parents elevates the risks for the offspring, the issue regarding the relative merits of a genetic hypothesis as opposed to an environmental hypothesis remains to be resolved (Calne *et al.*, 1987; Goldman and Tanner, 1998; Sveinbjörnsdottir *et al.*, 2000). Through the application of a so-called Hazard rate of PD function (cf. de la Fuente-Fernández, 2000) it has been tabulated that the risk associated with maternal PD was not dependent upon the age-of-onset of the afflicted mother but rather upon the age of the child at that time, i.e. the emergence of PD symptoms in the mother: the younger the child at the time-of-onset of the mother's symptoms, the higher the risk for Parkinsonism in the child (de la Fuente-Fernández and Calne, 2002). However, as the authors indicate (ibid), there is much evidence to support the presence of a genetic predisposition. For example, idiopathic Parkinsonism evolves from the 'incidental Lewy body state' through which some individuals remain without the symptoms of the disorder despite the presence of Lewy bodies in their substantia nigra (Golbe *et al.*, 1993; de la Fuente-Fernández and Calne, 1996; de la Fuente Fernández *et al.*, 1998), with prevalence rates that reach a plateau at advanced ages

(Gibb and Lees, 1988), at which period the prevalence of 'incidental Lewy body state' reaches 15% of the general population. The high prevalence implies that a genetic background to the disorder may mean the existence of genetic polymorphism (Cavalli-Sforza and Bodmer, 1971), prompting the consideration: genetic polymorphism confers a predisposition and the state of disorder occurs first when an adverse environmental situation is superimposed. The very real incidence of genetic polymorphisms associated with Lewy body pathology (Payami *et al.*, 1995; Scott *et al.*, 2001) nevertheless appear insufficient to provide a genetic etiology. Recent evidence by Kuopio *et al.* (2001) examining a cohort of PD patients and matched controls, from a large area of southwestern Finland (with a total population of 196,864), concluded that familial PD may not necessarily be indicative of a genetic mechanism in the etiology of PD. The authors (ibid) suggested that shared environment with common risk factors may be more important (see also Wang *et al.*, 1993; Vieregge *et al.*, 1994; De Michele *et al.*, 1996; Liou *et al.*, 1997; Uitti *et al.*, 1997; Kuopio *et al.*, 1999). α-Synuclein is identified in the post-mortem brains of both familial PD and idiopathic PD patients (Baba *et al.*, 1998; Spillantini *et al.*, 1997. α-synuclein has a putative role in the neurodegenerative disorders, namely evoking DA neuron neurotoxicity *in vivo* and *in vitro*.

GENE INVOLVEMENT IN EPILEPSY AND ATAXIA

Gil-Nagel (2003) characterises epilepsy as a cluster disorder, encompassing different etiologies, prognoses and therapeutic implications, and accompanied by different pathogeneses ultimately leading to the expression of an increased excitability or decreased inhibition of cortical (or limbic-cortical) neurons and repetitive spontaneous firing. The review examines the avenues of epileptogenesis mechanism: ion channel abnormalities (see below), excitotoxic neuronal damage as in mesial temporal sclerosis, and malformations of cortical development. In this array, several indications of inherited characteristics are reviewed, with particular reference to the gene loci involved (Cambardella *et al.*, 2000; Phillips *et al.*, 1995; 2002).

Despite a multitude of animal models for testing the neurobiological bases for epilepsy and the involvement of mutations in brain P/Q-type voltage-gated calcium (Ca^{++}) channels, the genetic basis of the movement disorder in humans remains unidentified. Spontaneously-occurring mutant mouse models, such as leaner, lethargic, staggerer, stargazer and tottering mice (Fletcher and Frankel, 1999), are available with mutations in the genetic coding for subunits providing the configurations for neuronal membrane P/Q-type voltage-gated Ca^{++} ion channels; these mouse models demonstrate several anomalies associated with the disease states, e.g. absence epilepsy, cerebellar degeneration and ataxia. P/Q-type Ca^{++} channels are widely expressed in the mammalian brain in a predominantly presynaptic distribution (Westenbroek *et al.*, 1995). In conjunction with action potential conductance these channels exert a major influence on modulation of neurotransmitter release (Regehr and Mintz, 1994). Ion channel gene mutations may be implied in certain paroxysmal neurologic conditions, e.g. brain K^+ and Na^+ channels may be implicated (Charlier *et al.*, 1998; Hanna *et al.*, 1998; Singh *et al.*, 1998; Wallace *et al.*, 1998). Recently, Jouvenceau *et al.* (2001) identified a boy of 11 years with a phenotype consisting of primary generalised epilepsy; and episodic epilepsy, characterised by severe and extended attacks of cerebellar ataxia and dysarthria, and progressive ataxia. Primary generalised epilepsy, includes both generalised tonic-clonic seizures without warning, and frequent absence attacks. Note that electroencephalographic abnormalities have been indicated in acetazolamide-responsive paroxysmal ataxia (van Bogaert and Szliwowski, 1996), even though epilepsy does not always accompany episodic ataxia. The features of the ataxia episodes were identical to those of patients with episodic ataxia type-2, thereby implying some alteration of genetic coding underlying the P/Q-type Ca^{++} channel. Patients suffering from episodic ataxia usually develop a progressive interictal cerebellar syndrome following on cerebellar damage (Griggs *et al.*, 1978), as for example displayed by magnetic resonance structural imaging of vermian atrophy (Vighetto *et al.*, 1988). Since several studies have pointed at mutations that lead to aberrations of the P/Q-type Ca^{++} channels (Ophoff *et al.*, 1996; Yue *et al.*, 1997; 1998; Denier *et al.*, 1999), Jouvenceau *et al.* (2001) sequenced the coding region of the CACNA1A gene (localised on chromosome 19p) in the child presenting early-onset absence epileplsy and cerebellar ataxia. They discovered a previously-undescribed heterogenous point mutation in the CACNA1A gene that resulted in complete loss of the C terminal region of the pore-forming subunit and eventually impairing Ca^{++} channel function. Thus, a modification of genetic configuration in human absence epilepsy, as expressed by one 11-year-old patient, appears to be associated with dysfunction of P/Q-type voltage-gated Ca^{++} ion channels in the brain, and the patient's phenotype resembles that of certain mouse mutation models showing distortions of synaptic/neuronal transmission (Wakamori *et al.*, 1998; Caddick *et al.*, 1999; Ayata *et al.*, 2000), for example leading to abnormalities in corti-

cothalamic network synchrony (Huntsman *et al.*, 1999).

CRITICAL SITES OF PATHOLOGY IN MULTIPLE SCLEROSIS

Bjartmar and Trapp (2003) have outlined several factors in the histopathology of multiple sclerosis (MS), including intracellular inflammation, demyelination, reactive astrogliosis and axonal degeneration. Thus, much evidence, utilising both analytical and morphological applications, has accumulated to both describe and differentiate the processes underlying axonal destruction in the disorder (e.g. Ferguson *et al.*, 1997; Narayana *et al.*, 1997, 1998; Matthews *et al.*, 1998; Trapp *et al.*, 1998, 1999; van Waesberghe *et al.*, 1999; Bjartmar and Trapp, 1999, 2001; Ganter *et al.*, 1999; Scherer, 1999; Stevenson and Miller, 1999). The propensity of the brain and CNS for compensatory actions (not least, an important aspect of neurodevelopment) is hardly more succinctly demonstrated than under conditions of progressive axonal injury and degeneration (Rudick *et al.*, 1999), whereby it has been observed that in individuals with MS lesions bearing an average axonal loss of 64% there was absence of signs of clinical impairment (Mews *et al.*, 1998), attributable to site of lesion, neuronal redundancy, moderate total axon loss and remyelination (cf. Bjartmar and Trapp, 2003). There exists a certain role for inheritance in MS since a constellation of genes, coding for myelin-related proteins, such as MAG, PLP, PMP22, P0 and connexin, whose presence make relative contributions to the long-term viability of axonal longevity (e.g. Anzini *et al.*, 1997; Griffiths *et al.*, 1998; Yin *et al.*, 1998; Sahenk *et al.*, 1999; but see also Rufer *et al.*, 1996).

PITFALLS AND WINDFALLS OF A DEVELOPING BRAIN

Although the genetic associations in idiopathic diseases remain unclear (Olanow and Tatton, 1999; Zoghbi and Orr, 2000), the existence of neuron pathology similarities as suggested by disorders involving single identified genetic mutations, e.g. Huntington's disease, or identification of familial hereditary components, e.g. PD, signify the molecular convolutions inherent to the processes of cell death (Schulz and Dichgans, 1999). In their turn the adaptive processes following cell death, particularly in the very young but often in the adult after chronic administration, are shown to produce constellations of neurochemical changes and dysfunction. A neurodevelopmental strategy in studying brain disorders emphasises the state of dynamic equilibrium in a *constantly-developing* brain. As postulated by Armstrong and Barker (2001) a primary deficit in neural stem-cell proliferation, migration, or differentiation, or both, may contribute to the net cell loss and neuronal circuit disruption expressed in the disorders.

Acknowledgements

We are grateful for the support provided by the Cerebro y Mente Foundation, Madrid, Spain.

References

Abe K, K Taguchi, T Wasai, J Ren, I Utsunomiya, T Shinohara, T Miyatake and T Sano (2001a) Stereoselective effect of (*R*)- and (*S*)-1-methyl-1,2,3,4-tetrahydroisoquinolines on a mouse model of Parkinson's disease. *Brain Res. Bull.* **56**, 55-60.

Abe K, K Taguchi, T Wasai, J Ren, I Utsunomiya, T Shinohara, T Miyatake and T Sano (2001b) Biochemical and pathological study of endogenous 1-benzyl-1,2,3,4-tetrahydroisoquinoline-induced parkinsonism in the mouse. *Brain Res.* **907**, 134-138.

Abeliovich A, Y Schmitz, I Farinas, D Choi-Lundberg, W-H Ho, PE Castillo, N Shinsky, JMG Verdugo, M Armanini, A Ryan, M Hynes, H Pkillips, D Sulzer and A Rosenthal (2000) Mice lacking α-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron* **25**, 239-252.

Ahlskog JE and MD Muenter (2000) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov. Disord.* **16**, 448-458.

Albert TJ, CW Dempesy and CA Sorenson (1985) Anterior cerebellar vermal stimulation: effect on behaviour and basal forebrain neurochemistry in rat. *Biol. Psychiatr.* **20**, 1267-1276.

Alexi T, JL Venero and F Hefti (1997) Protective effects of neurotrophin-4/5 and transforming growth factor-alpha on striatal neuronal phenotypic degeneration after excitotoxic lesioning with quinolinic acid. *Neuroscience* **78**, 73-86.

Allen SM and WM Davis (1999) Relationship of dopamine to serotonin in the neonatal 6-OHDA rat model of Lesch-Nyhan syndrome. *Behav. Pharmacol.* **10**, 467-474.

Altman J and SA Bayer (1997) Development of the cerebellar system in relation to its evolution, structure, and functions. *CRC Press*, Boca Raton, Fl.

Antkiewicz-Michaluk L, A Szczudlik, A Krygowska-Wajs, I Romanska and J Vetulani (1997) Increase in salsolinol level in the cerebrospinal fluid of parkinsonian patients is related to dementia: advantage of a new high-performance liquid chromatography methodology. *Biol. Psychiatr.* **42**, 514-518.

Antkiewicz-Michaluk L, I Romanska, I Papla, J Michaluk, M Bakalarz, J Vetulani, A Krygowska-Wajs and A Szczudlik (2000) Neurochemical changes induced by acute and chronic administration of 1,2,3,4-tetrahydroisoquinoline and salsolinol in dopaminergic structures of rat brain. *Neuroscience* **96**, 59-64.

Antkiewicz-Michaluk L, J Michaluk, M Mokrosz, I Romanska, E Lorenc-Koci, S Ohta and J Vetulani (2001) Different action on dopamine catabolic pathways of two endogenous 1,2,3,4-tetrahydroisoquinolines with similar antidopaminergic properties. *J. Neurochem.* **78**, 100-108.

Anzini P, DH Neuberg, M Schachner, E Nelles, K Willeke, J Zielasek,

KV Toyka, U Suter and R Martini (1997) Structural abnormalities and deficient maintainence of peripheral nerve myelin in mice lacking the gap junction protein connexin 32. *J. Neurosci.* **17**, 4545-4551.

Araujo DM, JG Chabot and R Quirion (1990) Potential neurotrophic factors in the mammalian central nervous system: functional significance in the developing and aging brain. *Int. Rev. Neurobiol.* **32**, 141-174.

Araujo DM and DC Hilt (1997) Glial cell line-derived neurotrophic factor attenuates the excitotoxin-induced behavioural and neurochemical deficits in a rodent model of Huntington's disease. *Neuroscience* **81**, 1099-1110.

Archer T and A Fredriksson (1992) Functional changes implicating dopaminergic systems following prenatal treatments. *Dev. Pharmacol. Ther.* **18**, 201-222.

Archer T and A Fredriksson (2000) Restoration and putative protection in parkinsonism. *Neurotoxicity Res.* **2**, 251-292.

Archer T, W Danysz, A Fredriksson, G Jonsson, J Luthman, E Sundström and A Teiling (1988) Neonatal 6-hydroxydopamine-induced dopamine depletions: motor activity and performance in maze learning. *Pharmacol. Biochem. Behav.* **31**, 357-364.

Archer T, T Palomo and A Fredriksson (2002) Neonatal 6-hydroxydopamine-induced hypo/hyperactivity: blockade by dopamine. *Neurotoxicity Res.* **4**, 247-266.

Archer T, T Palomo, R McArthur and A Fredriksson (2003a) Effects of acute administration of DA agonists on locomotor activity: MPTP versus neonatal intracerebroventricular 6-OHDA treatment. *Neurotoxicity Res.* **5**, 95-110.

Archer T, N Schröder and A Fredriksson (2003b) Neurobehavioural deficits following postnatal iron overload: II Instrumental learning performance. *Neurotoxicity Res.* **5**, 77-94.

Armstrong RJE and RA Barker (2001) Neurodegeneration: a failure of regeneration? *Lancet* **358**, 1174-1176.

Arndt S, NC Andreasen, M Flaum, D Miller and P Nopoulos (1995) A longitudinal study of symptom dimensions in schizophrenia. Prediction and patterns of change. *Arch. Gen. Psychiatr.* **52**, 352-360.

Ayala A, J Parrado, J Cano and A Machado (1994) Reduction of 1-methyl-1,2,3,4-tetrahydroisoquinoline level in substantia nigra of the aged rat. *Brain Res.* **638**, 334-336.

Ayata C, M Imizu-Sasamata, EH Lo *et al.* (2000) Impaired neurotransmitter release and elevated threshold for cortical spreading depression in mice with mutations in the β1A subunit of P/Q type Ca^{2+} channels. *Neuroscience* **95**, 639-645.

Aylward EH, AL Reiss, MJ Reader, HS Singer, JE Brown and MB Denckla (1996) Basal ganglia volumes in children with attention-deficit hyperactivity disorder. *J. Child Neurol.* **11**, 112-115.

Baba M, S Nakajo, PH Tu, T Tomita, K Nakaya, VM Lee, JQ Trojanowski and T Iwatsubo (1998) Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. *Am. J. Pathol.* **152**, 879-884.

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol. Bull.* **121**, 65-94.

Barkley RA (1998) Attention-deficit hyperactivity disorder. *Sci. Am.* **279**, 43-50.

Baumgardner TL, HS Singer, MB Denckla, MA Rubin, MT Abrams, MJ Colli and AL Reiss (1996) Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. *Neurology* **47**, 477-482.

Ben-Shachar D and MBH Youdim (1991) Intranigral iron injection induces behavioral and biochemical "parkinsonism" in rats. *J. Neurochem.* **57**, 2133-2135.

Ben-Shachar D, G Eshel, JP Finberg and MBH Youdim (1991) The iron chelator desferrioxamine (Desferal) retards 6-hydroxydopamine-induced degeneration of nigrostriatal dopamine neurons. *J. Neurochem.* **56**, 1441-1444.

Bennett MC, JF Bishop, Y Leng, TN Chase and MM Mouradian (1999) Degradation of a-synuclein by proteasome. *J. Biol. Chem.* **274**, 33855-33858.

Berquin PC, JN Giedd, LK Jacobsen, SD Hamburger, AL Krain, JL Rapoport and FX Castellanos (1998) Cerebellum in attention-deficit hyperactivity disorder – a morphometric MRI study. *Neurology* **50**, 1087-1093.

Bessler H, R Djaldetti, H Salman, M Bergman and M Djaldetti (1999) IL-1β, IL-2, IL-6 and TNF-α production by peripheral blood mononuclear cells from patients with Parkinson's disease. *Biomed. Pharmacother.* **53**, 141-145.

Bezzi P, M Domercq, L Brambilla, R Galli, D Schols, E De Clercq, A Vescovi, G Bagetta, G Kollias, J Meldolesi and A Volterra (2001) CXCR4-activated astrocyte glutamate release via TNFa: amplification by microglia triggers neurotoxicity. *Nature Neurosci.* **4**, 702-710.

Bigham R, R Copes and L Srour (2002) Exposure to thimerosal in vaccines used in Canadian infant immunization programs, with respect to risk of neurodevelopmental disorders. *Can. Commun. Dis. Rep.* **28**, 69-80.

Bjartmar C and BD Trapp (2001) Axonal and neuronal damage in multiple sclerosis: mechanisms and functional consequences. *Curr. Opin. Neurol.* **14**, 271-278.

Bjartmar C and BD Trapp (2003) Axonal degeneration and progressive neurologic disability in multiple sclerosis. *Neurotoxicity Res.* **5**, 157-164.

Bjartmar C, X Yin and B Trapp (1999) Axonal pathology in myelin disorders. *J. Neurocytol.* **28**, 383-395.

Blanchet PJ, SM Papa, LV Metman, MM Mouradian and TN Chase (1997) Modulation of levodopa-induced motor response complications by NMDA antagonists in Parkinson's disease. *Neurosci. Biobehav. Rev.* **21**, 447-453.

Blanchet PJ, S Konitsiotis and TN Chase (1998) Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Mov. Disord.* **13**, 798-802.

Boka G, P Anglade, D Wallach, F Javoy-Agid, Y Agid and EC Hirsch (1994) Immunocytochemical analysis of tumour necrosis factor and its receptors in Parkinson's disease. *Neurosci. Lett.* **172**, 151-154.

Bordet R, S Ridray, S Carboni, J Diaz, P Sokoloff and J-C Schwartz (1997) Induction of dopamine D_3 receptor expression as a mechanism of behavioural sensitisation to levodopa. *Proc. Natl. Acad. Sci. USA* **94**, 3363-3367.

Bowenkamo KE, AF Hoffman, GA Gerhardt, MA Henry, PT Biddle *et al.* (1995) Glial cell line-derived neurotrophic factor supports survival of injured midbrain dopaminergic neurons. *J. Comp. Neurol.* **355**, 479-489.

Breese GR, A Baumeister, TJ McCown, SG Emerick, GD Frye, K Crotty and RA Mueller (1984) Behavioural differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. *J. Pharm. Exp. Ther.* **231**, 343-354.

Butterfield PG, BG Valanis, PS Spencer, CA Lindeman and JG Nutt (1993) Environmental antecedents of young-onset Parkinson's disease. *Neurology* **43**, 1150-1158.

Caddick SJ, C Wang, CF Fletcher *et al.* (1999) Excitatory but not

inhibitory synaptic transmission is reduced in lethargic (Cacnb4(1h)) and tottering (Cacna 1 a tg) mouse thalami. *J Neurophysiol* **81**, 2066-2074.

Calabresi P, P Giacomini, D Centonze and G Bernardi (2000) Levodopa-induced dyskinesia: a pathological form of striatal synaptic plasticity? *Ann. Neurol.* **47**(Suppl.1), 60-68.

Calne S, B Schoenberg, W Martin, RJ Uitti, P Spencer and DB Calne (1987) Familial Parkinson's disease: possible role of environmental factors. *Can. J. Neurol. Sci.* **14**, 303-305.

Cambardella A, G Annesi, M DeFusco, A Patrignani, U Aguglia, F Annesi, AA Pasqua, P Spadafora, RL Oliveri, P Valentino, M Zappia, A Ballabio, G Casari and A Ouattrone (2000) A new locus for autosomal dominant nocturnal frontal lobe epilepsy maps to chromosome 1. *Neurology* **55**, 1467-1471.

Casey BJ, FX Castellanos, JN Giedd, WL Marsh, SD Hamburger, AB Schubert, YC Vauss, AC Vaituzis, DP Dickstein, SE Sarfatti and JL Rapoport (1997) Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am. Acad. Child Adolesc. Psychiatry* **36**, 374-383.

Castellanos FX, JN Giedd, WL Marsh *et al.* (1996) Quantitative brain resonance imaging in attention deficit hyperactivity disorder. *Arch. Gen. Psychiat.* **53**, 607-616.

Cavalli-Sforza LL and WF Bodmer (1971) The genetics of human populations. WH Freeman: San Francisco.

Centonze D, B Picconi, P Gubellini, G Bernardi and P Calabresi (2001) Dopaminergic control of synaptic plasticity in the dorsal striatum. *Eur. J. Neurosci.* **6**, 1071-1077.

Chang LW, RR Reuhl and JM Spyker (1977a) Ultrastructural study of the latent effects of methylmercury on the nervous system after prenatal exposure. *Environ. Res.* **13**, 171-185.

Chang LW, RR Reuhl and GW Lee (1977b) Degenerative changes in the developing nervous system as a result of in utero exposure to methylmercury. *Environ. Res.* **14**, 414-423.

Charlier C, NA Singh, SG Ryan *et al.* (1998) A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nature Genet.* **18**, 53-55.

Chase, T.N. and Oh, J.D. (2002) Striatal mechanisms and pathogenesis of parkinsonian signs and motor complications. *Ann. Neurol.* **4**[Suppl. 1], 122-129.

Chase TN, F Bibbiani and JD Oh (2003) Striatal glutamatergic mechanisms and extrapyramidal movement disorders. *Neurotoxicity Res.* **5**, 139-146.

Chauhan NB, GJ Siegel and JM Lee (2001) Depletion of glial cell line-derived neurotrophic factor in substantia nigra neurons of Parkinson's disease brain. *J. Chem. Neuroanat.* **4**, 277-288.

Choi-Lundberg DL, Q Lin, Y-N Chang, YL Chiang, CM Hay, H Mojajeri, BL Davidson and MC Bohn (1997) Dopaminergic neurons protected from degeneration by GDNF gene therapy. *Science* **275**, 838-841.

Chun HS, JJ Son and JH Son (2000) Identification of potential compounds promoting BDNF production in nigral dopaminergic neurons: clinical implication in Parkinson's disease. *Neuroreport* **3**, 511-514.

Cierpial MA, DE Shasby, CA, Murphy, AH Borom, RE Stewart, SE Swithers and R McCarty (1989) Open-field behaviour of spontaneously hypertensive and Wistar-Kyoto normotensive rats: effects of reciprocal cross-fostering. *Behav. Neural Biol.* **51**, 203-210.

Clayton DF and JM George (1999) Synucleins in synaptic plasticity and neurodegenerative disorders. *J. Neurosci. Res.* **58**, 120-129.

Connor B and M Dragunow (1998) The role of neuronal growth factors in neurodegenerative disorders of the human brain. *Brain Res. Brain Res. Rev.* **27**, 1-39.

Conway KA, JD Harper and PT Lansbury (1998) Fibrils formed *in vitro* from a-synuclein and two mutant forms linked to Parkinson's disease are typical amyloid. *Nature Med.* **4**, 1318-1320.

Danielsson BRG, A Fredriksson, L Dahlgren, A Teiling-Gårdlund, L Olsson, L Dencker and T Archer (1993) Behavioural effects of prenatal metallic mercury exposure in rats. *Neurotoxicol. Teratol.* **15**, 391-396.

Davison AN and J Dobbing (1968) *Applied Neurochemistry* (Blackwell: Oxford), pp 178-221.

De la Fuenta-Fernández R (2000) Maternal effect on Parkinson's disease. *Ann. Neurol.* **48**, 782-787.

De la Fuenta-Fernández R and DB Calne (1996) What do Lewy bodies tell us about dementia and Parkinsonism, In: Perry RH, IG McKeith and EK Perry, Eds., Dementia with Lewy bodies (Cambridge University Press: New York), pp 287-301.

De la Fuenta-Fernández R. and DB Calne (2002) Evidence for environmental causation of Parkinson's disease. *Parkinsonism Relat Disord* **8**, 235-241.

De la Fuenta-Fernández R, M Schulzer, E Mak, A Kishore and DB Calne (1998) The role of the Lewy body in idiopathic Parkinsonism. *Parkinsonism Relat. Disord.* **4**, 73-77.

De Michele G, A Filla, G Volpe *et al.* (1996) Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. *Mov. Disord.* **11,** 17-23.

De Yebenes JG, R Sanchez-Pernaute, JM Garrido, A Rábano, J Albisua, A Rojo *et al.* (1998) Long-term intracerebral infusion of fibroblast growth factors restores motility and enhances F-DOPA uptake in parkinsonian monkeys. *Parkinsonism Rel. Disord.* **4**, 147-158.

De Yebenes JG, M Sanchez and MA Mena (2003) Neurotrophic factors for the investigation and treatment of movement disorders. *Neurotoxicity Res.* **5** 119-137.

Del Dotto P, N Pavese, G Gambaccini, S Bernardini, LV Metman, TN Chase and U Bonuccelli (2001) Intravenous amantadine improves levodopa-induced dyskinesias: an acute double-blind placebo-controlled study. *Mov. Disord.* **16**, 515-520.

Dempesy CW, DM Tootle, CJ Fontana, AT Fitzjarrell, RE Garey and RG Heath (1984) Stimulation of the paleocerebellar cortex of the cat: increased rate of synthesis and release of catecholamines at limbic sites. *Biol. Psychiatr.* **18**, 127-132.

Denckla MB (1993) The child with developmental disabilities grown up: adult residua of childhood disorders. *Neurol. Clin.* **11**, 105-125.

Denckla MB (1996) Biological correlates of learning and attention: what is relevant to learning disability and attention-deficit hyperactivity disorder? *J. Dev. Behav. Pediatr.* **17**, 114-119.

Deng Y, W Maruyama, M Kawai, P Dostert, H Yamamura, T Takahashi and M Naoi (1997) Assay for the (*R*)- and (*S*)- enantiomers of salsolinols in biological samples and foods with ion-pair high-performance liquid chromatography using beta-cyclodextrin as a chiral mobile phase additive. *J. Chromatogr. B. Biomed. Sci. Appl.* **689**, 313-320.

Denier C, A Ducros, K Vahedi *et al.* (1999) High prevalence of CACNA1A truncations and broader clinical spectrum in episodic ataxia type 2. *Neurology* **52**, 1816-1821.

Descarries L, JJ Soghomonian, S Garcia, G Doucet and JP Bruno (1992) Ultrastructural analysis of the serotonin hyperinnervation in adult rat neostriatum following neonatal dopamine denervation with 6-hydroxydopamine. *Brain Res.* **569**, 1-13.

Dostert P, M Strolin Benedetti, F Della Vedova, CF Allievi, R La Croix, G Dordain, D Vernay and F Durif (1993) Dopamine-derived tetrahydroisoquinolines and Parkinson's disease. *Adv.*

Neurol. **60**, 218-223.

Double K, P Riederer and M Gerlach (1999) The significance of neuromelanin in Parkinson's disease. *Drug News Develop.* **12**, 333-340.

Dougherty DD, AA Bonab, TJ Spencer, SL Rauch, BK Madras and AJ Fischman (1999) Dopamine transporter density in patients with attention deficit disorder. *Lancet* **354**, 2132-2133.

Douglas RJ, GM Clark, LC Erway, DG Hubbard and CG Wright (1979) Effects of vestibular genetic defects on behavior related to spatial orientation and emotionality. *J. Comp. Physiol. Psychol.* **93**, 467-480.

Engelender S, Z Kaminsky, X Guo, AH Sharp, RK Amaravi, JJ Kleiderlein, RL Margolis, JC Troncoso, AA Lanahan, PF Worley, VL Dawson, TM Dawson and CA Ross (1999) Synphilin-1 associates with a-synuclein and promotes the formation of cytosolic inclusions. *Nature Genet.* **22**, 110-114.

Faraj BA, VM Camp and RL Watts (1990) Effect of adrenal-caudate transplantation on CSF levels of salsolinol sulfate in patients with Parkinson's disease. *J. Neural Transm.* **32**, 481-484.

Faraj BA, VM Camp and M Kutner (1991) Interrelationship between activation of dopaminergic pathways and cerebrospinal fluid concentration of dopamine tetrahydroisoquinoline metabolite salsolinol in humans: preliminary findings. *Alcohol Clin. Exp. Res.* **15**, 86-89.

Ferguson B, MK Matyszak, MM Esiri and VH Perry (1997) Axonal damage in acute multiple sclerosis lesions. *Brain* **120**, 393-399.

Figurov A, LD Pozzo-Miller, P Olafsson, T Wang and B Lu (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* **381**, 706-709.

Fletcher CF and WN Frankel (1999) Ataxic mouse mutants and molecular mechanisms of absence epilepsy. *Hum. Mol. Genet.* **8**, 1907-1912.

Frankish H (2001) Report finds no link between thimerosal and neurodevelopmental disorders. *Lancet* **358**, 1163.

Fredriksson A and T Archer (1997) Alpha-phenyl-tert-butyl-nitrone (PBN) reverses age-related maze learning performance and motor activity deficits in mice. *Behav. Pharmacol.* **7**, 1-9.

Fredriksson A and T Archer (2002) Functional alteration by NMDA antagonist: effects of L-Dopa, neuroleptic drugs and postnatal administration. *Amino Acids* **23**, 111-132.

Fredriksson A and T Archer (2003) Effect of postnatal iron administration on MPTP-induced behavioural deficits and neurotoxicity: Behavioural enhancement by L-Dopa-MK-801 co-administration. *Behav. Brain Res.* in press.

Fredriksson A, L Dahlgren, B Danielsson, P Eriksson, L Dencker and T Archer (1992) Behavioural effects of neonatal metallic mercury exposure in rats. *Toxicology*, **74**, 151-160.

Fredriksson A, A Teiling Gårdlund, K Bergman, A Oskarsson, B Ohlin, B Danielsson and T Archer (1993) Effects of maternal dietary supplementation with selenite on the postnatal development of rat offspring exposed to methyl mercury *in utero*. *Pharmacol. Toxicol.* **72**, 377-382.

Fredriksson A, L Dencker, T Archer and BR Danielsson (1996) Prenatal coexposure to metallic mercury vapour and methylmercury produce interactive behavioural changes in adult rats. *Neurotoxicol. Teratol.* **18**, 129-34.

Fredriksson A, N Schröder, P Eriksson, I Izquierdo and T Archer (1999) Neonatal iron exposure induces neurobehavioural dysfunctions in adult mice. *Toxicol. Appl. Pharmacol.* **159**, 25-30.

Fredriksson A, N Schröder, P Eriksson, I Izquierdo and T Archer (2000) Maze learning and motor activity deficits in adult mice induced by iron exposure during a critical postnatal period. *Brain Res. Dev. Brain Res.* **119**, 65-74.

Fredriksson A, N Schröder, P Eriksson, I Izquierdo and T Archer (2001) Neonatal iron potentiates adult MPTP-induced neurodegenerative and functional deficits. *Parkinsonism Relat. Disorders* **7**, 97-105.

Fredriksson A, N Schröder and T Archer (2003) Neurobehavioural deficits following postnatal iron overload: I Spontaneous motor activity. *Neurotoxicity Res.* **5**, 53-76.

Gainetdinov RR, WC Wetsel, SR Jones, ED Levin, M Jaber and MG Caron (1999) Role of serotonin in the paradoxical calming effect of psychomotor stimulants on hyperactivity. *Science* **283**, 397-401.

Ganter P, C Prince and MM Esiri (1999) Spinal cord axonal loss in multiple sclerosis: a post-mortem study. *Neuropathol. Appl. Neurobiol.* **25**, 459-467.

Gerhardt GA, WA Cass, P Huettl, S Brock, Z Zhang and DM Gash (1999) GDNF improves dopamine function in the substantia nigra but not the putamen of unilateral MPTP-lesioned rhesus monkeys. *Brain Res.***817**, 163-171.

Gerlach M, D Ben-Schachar, P Riederer and MBH Youdim (1994) Altered brain metabolism of iron as a cause of neurodegenerative diseases? *J. Neurochem.* **67**, 793-807.

Gerlach M, K Double, P Riederer, E Hirsch, K Jellinger, P Jenner, A Trautwein and MBH Youdim (1997) Iron in the Parkinsonian substantia nigra (letter). *Movem. Dis.* **12**, 258-260.

Gerlach M, KL Double, D Ben-Shachar, L Zecca, MBH Youdim and P Riederer (2003) Neuromelanin and its interaction with iron as a potential risk factor for dopaminergic neurodegeneration underlying Parkinson's disease. *Neurotoxicity Res.* **5**, 35-44.

Giasson BI, K Uryu, JQ Trojanowski and VM Lee (1999) Mutant and wild-type human α-synucleins assemble into elongated fibrils with distinct morphologies *in vitro*. *J. Biol. Chem.* **274**, 7619-7622.

Gibb WRG and AJ Lees (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J. Neurol. Neurosurg. Psychiatr.* **51**, 745-752.

Gil-Nagel A (2003) Neurodevelopmental liabilities in epilepsy. *Neurotoxicity Res.* **5**, 45-52.

Giros B, M Jaber, RM Wightman and MG Caron (1996) Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* **379**, 606-612.

Golbe LI, AM Lazzarini, KO Schwarz, MH Mark, DW Dickson and RC Duvoisin (1993) Autosomal dominant parkinsonism with benign course and typical Lewy body pathology. *Neurology* **43**, 2222-2227.

Golbe LI, G Di Iorio, G Sanges *et al.* (1996) Clinical genetic analysis of Parkinson's disease in the Contursi kindred. *Ann. Neurol.* **40**, 767-775.

Goldman SM and C Tanner (1998) In: . Jankovic J and E Tolosa, Eds., Etiology of Parkinson's disease, 3rd edition, (Williams and Wilkins: Baltimore), pp 133-158.

Gong L and RM Kostrzewa (1992) Supersensitized oral response to a serotonin agonist in neonatal 6-OHDA treated rats. *Pharmacol. Biochem. Behav.* **41**, 621-623.

Gong L, RM Kostrzewa, RW Fuller and KW Perry (1992) Supersensitization to the oral response to SKF 38393 in neonatal 6-OHDA-lesioned rats is mediated through a serotonin system. *J. Pharmacol. Exp. Ther.* **261**, 1000-1007.

Good P, W Olanow and D Perl (1992) Neuromelanin-containing neurons of the substantia nigra accumulate iron and aluminium in Parkinson's disease: a LAMMA study. *Brain Res.* **593**, 343-346.

Gorell JM, RJ Ordidge, GG Brown, JC Deniau, NM Buderer and JA Helpern (1995) Increased iron-related MRI contrast in the substantia nigra in Parkinson's disease. *Neurology* **45**, 1138-1143.

Graybiel AM (2000) The basal ganglia. *Curr. Biol.* **14**, 509-511.

Griffiths I, M Klugmann, T Anderson, D Yool, C Thomson, MH Schwab, A Schneider, F Zimmermann, M McCulloch, N Nadon and KA Neve (1998) Axonal swellings and degeneration in mice lacking the major proteolipid of myelin. *Science* **280**, 1610-1613.

Griffiths PD, BR Dobson, GR Jones and DT Clarke (1999) Iron in the basal ganglia in Parkinson's disease. An *in vitro* study using extended X-ray absorption fine structure and cryo-electron microscopy. *Brain* **122**, 667-673.

Griggs RC, RT Moxley, RA Lafrance *et al.* (1978) Hereditary paroxysmal ataxia: response to acetazolamide. *Neurology* **28**, 1259-1264.

Grunblatt E, S Mandel, G Maor and MBH Youdim (2001) Gene expression analysis in MPTP model of Parkinson's disease using cDNA microarray: effect of R-apomorphine. *J. Neurochem.* **78**, 1-12.

Gunne LM, JE Häggström and B Sjöquist (1984) Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. *Nature* **309**, 347-349.

Gunne LM, U Andersson, U Bondesson and P Johansson (1986) Spontaneous chewing movements in rats during acute and chronic antipsychotic drug administration. *Pharmacol. Biochem. Behav.* 25, 897-901.

Gunne LM, JE Häggström, P Johansson, ED Levin and L Terenius (1988) Neurobiochemical changes in tardive dyskinesia. *Enchephale* **14**, 167-173.

Gustafsson P, G Thernlund, E Ryding, I Rosen and M Cederblad (2000) Associations between cerebral blood-flow measured by single photon emission computed tomography (SPECT), electroencephalogram (EEG), behaviour symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder. *Acta Paediatr.* **89**, 830-835.

Hadjiconstantinou M, JG Fitkin, A Dalia and NH Neff (1991) Epidermal growth factor enhances striatal dopaminergic parameters in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mouse. *J. Neurochem.* **57**, 479-482.

Haines G, E Dietrichs, GA Mihailoff and EF McDonald (1997) The cerebellar-hypothalamic axis: basic circuits and clinical observations. *Int. Rev. Neurobiol.* **41**, 83-107.

Hamberger V and RN Openheim (1982) Naturally occurring neuronal death in vertebrates. *Neurosci. Comment* **1**, 39-55.

Hanna MG, NW Woodm and DM Kullmann (1998) Ion channels and neurological disease. *J. Neurol. Neurosurg. Psychiatr.* **65**, 427-431.

Hashimoto M and E Masliah (1999) Alpha-synuclein in Lewy body disease and Alzheimer's disease. *Brain Pathol.* **9**, 707-720.

Heffner TG and LS Seiden (1982) Possible involvement of serotonergic neurons in the reduction of locomotor hyperactivity caused by amphetamine in neonatal rats depleted of brain dopamine. *Brain Res.* **244**, 81-90.

Herzman C, M Wiens, D Bowering, B Snow and DB Calne (1990) Parkinson's disease: a case-control study of occupational and environmental risk factors. *Am. J. Ind. Med.* **17**, 349-355.

Herzman C, M Wiens, B Snow, S Kelly and DB Calne (1994) A case control study of Parkinson's disease in a horticultural region of British Columbia. *Mov. Disord.* **9**, 69-75.

Hirsch E, A Graybiel and Y Agid (1988) Melanized dopamine neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature* **334**, 345-348.

Ho SC, J Woo and CM Lee (1989) Epidemiologic study of Parkinson's disease in Hong Kong. *Neurology* **39**, 1314-1318.

Hsu LJ, M Mallory, Y Xia, I Veinbergs, M Hashimoto, M Yoshimoto, LJ Thal, T Saitoh and E Masliah (1998) Expression pattern of synucleins (non-Aβ component of Alzheimer's disease amyloid precursor protein/α-synuclein) during murine brain development. *J. Neurochem.* **71**, 338-344.

Huang N-Y, RM Kostrzewa, C Li, KW Perry and RW Fuller (**1997**) Persistent spontaneous oral dyskinesias in haloperidol-withdrawn rats neonatally lesioned with 6-hydroxydopamine: Absence of an association with the B_{max} for [^{3}H]raclopride binding to neostriatal homogenates. *J. Pharmacol. Exp. Ther.* **280**, 268-276.

Hubble JP, T Cao, RES Hassanein, JS Neuberger and WC Koller (1993) Risk factors for Parkinson's disease. *Neurology* **43**, 1693-1697.

Huntsman MM, DM Porcello, GE Homanics, TM DeLorey and JR Huguenard (1999) Reciprocal inhibitory connections and network synchrony in the mammalian thalamus. *Science* **283**, 541-543.

Hyman C, M Hofer, YA Barde, M Juhasz, GD Yancopoulos, SP Squinto and RM Lindsay (1991) BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* **350**, 230-232.

Igarashi K, Y Sugiyama, F Kasuya, K Saiki, T Yamakawa and S Ohata (1999) Determination of 1-methyl-1,2,3,4-tetrahydroisoquinoline in mouse brain after treatment with haloperidol by gas chromatography-selected ion monitoring. *J. Chromatogr. B. Biomed. Sci. Appl.* **731**, 53-58.

Ikonomidou C, F Bosch, M Miksa, P Bittigau, J Vöckler, K Dikranian KI Tenkova, V Stefovska, L Turski and JW Olney (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* **283**, 70-74.

Ikonomidou C, P Bittigau, MJ Ishimaru, DF Wozniak, C Koch, K Genz, MT Price, V Stefovska, F Hörster, T Tenkova, K Dikranian and JW Olney (2000) Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. *Science* **287**, 1056-1060.

Ishikawa A and S Tsuji (1996) Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. *Neurology* **47**, 160-166.

Ishiwata K, Y Koyanagi, K Abe, K Kawamura, T Taguchi, T Saitoh, J Toda, M Senda and T Sano (2001) Evaluation of neurotoxicity of TIQ and MPTP and of parkinsonism-preventing effect of 1-MeTIQ by *in vivo* measurement of pre-synaptic dopamine transporters and post-synaptic dopamine D(2) receptors in the mouse striatum. *J. Neurochem.* **79**, 868-876.

Itoh K, P Mehraein and S Weis (2000) Neuronal damage of the substantia nigra in HIV-1 infected brains. *Acta Neuropathol.* **99**, 376-384.

Iwai A, E Masliah, M Yoshimoto, N Ge, L Flanagan, HAR de Silva, A Kittel, and T Saitoh (1995) The precursor protein of non-AB component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. *Neuron* **14**, 467-475.

Jackson D and ED Abercrombie (1992) *In vivo* neurochemical evaluation of striatal serotonergic hyperinnervation in rats depleted of dopamine at infancy. *J. Neurochem.* **58**, 890-897.

Jackson-Lewis V, M Vila, R Djaldetti, C Guegan, G Liberatore, J Liu, KL O'Malley, RE Burke and S Przedborski (2000) Developmental cell death in dopaminergic neurons of the substantia nigra of mice. *J. Comp. Neurol.* **424**, 476-488.

Jellinger,KA (1999) The role of iron in neurodegeneration: prospects for pharmacotherapy of Parkinson's disease. *Drugs Aging* **14**, 115-140.

Jellinger KA, E Kienzel, G Rumpelmair, P Riederer, H Stachellberger, D Ben-Shachar and MBH Youdim (1992) Iron-melanin complex in substantia nigra of Parkinsonian brains: an X-ray microanalysis. *J. Neurochem.* **59**, 1168-1171.

Johnson AE, U Liminga, A Liden, N Lindefors, LM Gunne and FA Wiesel (1994) Chronic treatment with a classical neuroleptic alters excitatory amino acid and GABAergic neurotransmission in specific regions of the rat brain. *Neuroscience* **63**, 1003-1020.

Jouvenceau A, LH Eunson, A Spauschus, V Ramesh, SM Zuberi, DM Kullmann and MG Hanna (2001) Human epilepsy associated with the brain P/Q-type calcium channel. *Lancet* **358**, 801-807.

Kakigi T, XM Gao and CA Tamminga (1995) Drug-induced oral dyskinesias in rats after traditional and new neuroleptics. *J. Neural Transm. Gen. Sect.* **101**, 41-49.

Kalita J and UK Misra (2000) The substantia nigra is also involved in Japanese encephalitis. *Am. J. Neuroradiol.* **21**, 1978-1979.

Kaul M, GA Garden and SA Lipton (2001) Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature* **410**, 988-994.

Kerr BJ, EJ Bradbury, DHL Bennett, PM Triverdi, P Dassan, J French, DB Shelton, SB McMahon and SWN Thompson (1999) Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord. *J. Neurosci.* **19**, 5138-5148.

Kikuchi K, Y Nagatsu, Y Makino, T Mashino, S Ohta and M Hirobe (1991) Metabolism and penetration through blood-brain barrier of parkinsonism-related compounds, 1,2,3,4-tetrahydroisoquinoline and 1-methyl-1,2,3,4-tetrahydroisoquinoline. *Drug Metab. Dispos.* **19**, 257-262.

King JA, RA Barkley, Y Delville and CF Ferris (2000) Early androgen treatment decreases cognitive function and catecholamine innervation in an animal model of ADHD. *Behav. Brain Res.* **107**, 35-43.

Klitenick MA, CS Tham and HC Fibiger (1995) Cocaine and D-amphetamine increase c-fos expression in the rat cerebellum. *Synapse* **19**, 29-36.

Knardahl S and T Sagvolden (1979) Open-field behaviour of spontaneously hypertensive rats. *Behav. Neural Biol.* **27**, 187-200.

Kordower JH, EY Chen, C Winkler, R Fricker, V Charles, A Messing, EJ Mufson, SC Wong, JM Rosenstein, A Bjorklund, DF Emerich, J Hammang.and MK Carpenter (1997) Grafts of EGF-responsive neural stem cells derived from GFAP-hNGF transgenic mice; trophic and trophic effects in a rodent model of Huntington's disease. *J. Comp. Neurol.* **387**, 96-113.

Kordower JH, S Palfi, EY Chen, SY Ma, T Sendera, EJ Cochran, EJ Mufson, R Penn, CG Goetz and CD Comella (1999) Clinicopathological findings following intraventricular glial-derived neurotrophic factor treatment in a patient with Parkinson's disease. *Ann. Neurol.* **46**, 419-424.

Kordower JH, ME Emborg, J Bloch, SY Ma, Y Chu, L Leventhal, J McBride, EY Chen, S Palfi, BZ Roitberg, WD Brown, JE Holden, R Pyzalski, MD Taylor, P Carvey, Z Ling, D Trono, P Hantraye, N Deglon and Aebischer, P. (2000) Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. *Science* **290**, 767-773.

Korte M, P Carroll, E Wolf, G Brem, H Thoenen and T Bonhoeffer (1995) Hippocampal long-term potiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc. NatL. Acad. Sci. USA* **92**, 8856-8860.

Kostrzewa RM (1995) Dopamine receptor supersensitivity. *Neurosci. Biobehav. Rev.* **19**, 1-17.

Kostrzewa RM and JW Harper (1974) Effects of 6-hydroxydopa on catecholamine-containing neurons in brains of newborn rats. *Brain Res.* **69**, 174-181.

Kostrzewa RM, R Brus, KW Perry and RW Fuller (1993) Age-dependence of a 6-hydroxydopamine lesion on SKF 38393- and *m*-chlorophenylpiperazine-induced oral activity responses of rats. *Dev. Brain Res.* **76**, 87-93.

Kostrzewa RM, R Brus, JH Kalbfleisch, KW Perry and RW Fuller (1994) Proposed animal model of attention deficit hyperactivity disorder. *Brain Res. Bull.* **34**, 161-167.

Kostrzewa RM, TA Reader and L Descarries (1998) Serotonin neural adaptations to ontogenetic loss of dopamine neurons in rat brain. *J. Neurochem.* **70**, 889-898.

Kostrzewa RM, R Brus and KW Perry (1999a) Interactive modulation by dopamine and serotonin neurons of receptor sensitivity of the alternate neurochemical system. *Pol. J. Pharmacol.* **5**, 39-47.

Kostrzewa RM, R Brus, KW Perry and RW Fuller (1999b) Age-dependence of a 6-hydroxydopamine lesion on SKF 38393- and *m*-chlorophenylpiperazine-induced oral activity responses of rats. *Dev. Brain Res.* **76**, 87-93.

Kostrzewa RM, JP Kostrzewa and R Brus (2003) Dopamine receptor supersensitivity: an outcome and index of neurotoxicity. *Neurotoxicity Res.* **5**, 111-118.

Kotake Y, Y Tasaki, Y Makino, S Ohta and M Hirobe (1995) 1-Benzyl-1,2,3,4-tetrahydroisoquinoline as a parkinsonism-inducing agent: a novel endogenous amine in mouse brain and parkinsonian CSF. *J. Neurochem.* **65**, 2633-2638.

Kotake Y, M Yoshida, M Ogawa, Y Tasaki, M Hirobe and S Ohta (1996) Chronic administration of 1-benzyl-1,2,3,4-tetrahydroisoquinoline, an endogenous amine in the brain, induces parkinsonism in a primate. *Neurosci. Lett.* **217**, 69-71.

Krause KH, SH Dresel, J Krause, HF Kung and K Tatsch (2000) Increased striatal dopamine transport in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neurosci. Lett.* **285**, 107-110.

Krhger R, W Kuhn, T Müller, D Woitalla, M Graeber, S Kösel, H Prezuntek, J Epplen, L Schöls and O Reiss (1998) Ala30Pro mutation in the gene encoding a-synuclein in Parkinson's disease. *Nature Genet.* **18**, 106-108.

Kuopio A-M, RJ Marttila, H Helenius and UK Rinne (1999) Environmental risk factors in Parkinson's disease. *Mov. Disord.* **14**, 303-305.

Kuopio A-M, RJ Marttila, H Helenius and UK Rinne (2001) Familial occurrence of Parkinson's disease in a community-based case-control study. *Parkinsonism Rel. Dis.* **7**, 297-303.

Lammers CH, J Diaz, J-C Schwartz and P Sokoloff (2000) Seletive increase of dopamine D_3 receptor gene expression as a common effect of chronic antidepressant treatments. *Mol. Psychiatr.* **5**, 378-388.

Lärkfors L, A Oskarsson, J Sundberg and T Ebendal (1991) Methylmercury induced alterations in the nerve growth factor level in the developing brain. *Dev. Brain. Res.* **62**, 287-291.

Levi-Montalcini R (1966) The nerve growth factor: its mode of action on sensory and sympathetic nerve cells. *Harvey Lect.* **60**, 217-259.

Levi-Montalcini R (1987) The nerve growth factor 35 years later. *Science* **237**, 1154-1162.

Levi-Montalcini R and PU Angeletti (1968) Nerve growth factor. *Physiol. Rev.* **48**, 534-569.

Levine S (2002) Regulation of the hypothalamic-pituitary-adrenal axis in the neonatal rat: the role of maternal behavior. *Neurotoxicity Res.* **4**, 557-564.

Levine S, DM Lyons and AF Schatzberg (1997) Psychobiological con-

sequences of social relationships. *Ann. NY Acad. Sci.* **807**, 210-218.

Levivier M, S Przedborski, C Bencsics and UJ Kang (1995) Intrastriatal implantation of fibroblasts genetically engineered to produce brain-derived neurotrophic factor prevents degeneration of dopaminergic neurons in a rat model of Parkinson's disease. *J. Neurosci.* **15**, 7810-7820.

Lewander T (1994) Neuroleptics and the neuroleptic-induced deficit syndrome. *Acta Psychiatr. Scand. Suppl.* **380**, 8-13.

Lin LF, DH Doherty, JD Lile, S Bektesh and F Collins (1993) GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science* **260**, 1130-1132.

Lindström H, J Luthman, A Oskarsson, J Sundberg and L Olson (1991) Effects of long-term treatment with methylmercury on the developing brain. *Environ. Res.* **56**, 158-169.

Linert W, E Herlinger, RF Jameson, E Kienzl, KA Jellinger and MBH Youdim (1996) Dopamine, 6-hydroxydopamine, iron, and dioxygen—their mutual interactions and possible implication in the development of Parkinson's disease. *Biochim. Biophys. Acta* **1316**, 160-168.

Liou HH, MC Tsai, CJ Chen *et al.* (1997) Environmental risk factors and Parkinson's disease: a case control study in Taiwan. *Neurology* **48**, 1583-1588.

Lorenc-Koci E, M Smialowska, L Antkiewicz-Michaluk, K Golembiowska, M Bajkowska and S Wolfarth (2000) Effect of acute and chronic administration of 1,2,3,4-tetrahydroisoquinoline on muscle tone, metabolism of dopamine in the striatum and tyrosine hydroxylase immunocytochemistry in the substantia nigra in rats. *Neuroscience* **95**, 1049-1059.

Louis ED, LS Dure and S Pullman (2001) Essential tremor in childhood: a series of nineteen cases. Movem. Disord. 16, 921-923.

Lücking C, A Dürr, V Bonifati, J Vaughan, G De Michele, T Gasser, BS Harhangi, G Meco, P Denefle, N Wood, Y Agid and A Brice (2000) Association between early-onset Parkinson's disease and mutations in the Parkin gene. *New Engl. J. Med.* **342**, 1560-1567.

Luthman J, M Bassen, A Fredriksson and T Archer (1997) Functional changes induced by neonatal 6-hydroxydopamine lesions: effects of dose levels on behavioural parameters. *Behav. Brain Res.* **82**, 213-221.

Luthman J, B Bolioli, T Tsutsumi, A Verhofstad and G Jonsson (1987) Sprouting of serotonin nerve terminals following selective lesions of nigro-striatal dopamine neurons in the neonatal rat. *Brain Res. Bull.* **19**, 269-274.

Luthman J, A Fredriksson, T Lewander, G Jonsson and T Archer (1989) Effects of D-amphetamine and methylphenidate on hyperactivity produced by neonatal 6-hydroxydopamine treatment. *Psychopharmacology* **99**, 550-557.

Luthman J, A Fredriksson, A Plaznik and T Archer (1991) Ketanserin and mianserin treatment reverses hyperactivity in neonatally dopamine-lesioned rats. *J. Psychopharmacol.* **5**, 418-425.

Luthman J, E Lindqvist, D Young and R Cowburn (1990) Neonatal dopamine lesion in the rat results in enhanced adenylate cyclase activity without altering dopamine receptor binding or dopamine- and adenosine 3'-,5'-monophosphate-regulated (DARPP-32) immunoreactivity. *Exp. Brain Res.* **83**, 85-95.

Makino Y, S Ohta, O Tachikawa and M Hirobe (1988) Presence of tetrahydroisoquinoline and 1-methyl-tetrahydro-isoquinoline in foods: compounds related to Parkinson's disease. *Life Sci.* **43**, 373-378.

Maraganore DM, DJ Schaid, WA Rocca and AE Harding (1996) Anticipation in familial Parkinson's disease: a reanalysis of 13 United Kingdom kindreds. *Neurology* **47**, 1512-1517.

Marsden CD (1986) Parkinson's disease in twins. *J. Neurol. Neurosurg. Psychiatr.* **50**, 105-106.

Marttila RJ, J Kaprio, M Koskenvuo and UK Rinne (1988) Parkinson's disease in a nationwide twin cohort. *Neurology* **38**, 1217-1219.

Maruyama W, P Dostert, K Matsubara and M Naoi (1995) *N*-methylsalsolinol produces hydroxyl radicals: involvement to neurotoxicity. *Free Radic. Biol. Med.* **19**, 67-75.

Maruyama W, H Narabayashi, P Dostert and M Naoi (1996) Stereospecific occurence of a parkinsonism-inducing catechol isoquinoline, *N*-methyl-(*R*)-salsolinol, in the human intraventricular fluid. *J. Neural Transm.* **103**, 1069-1076.

Maruyama W, M Naoi, T Kasamatsu, Y Hashizume, T Takahashi, K Kohda and P Dostert (1997a) An endogenous dopaminergic neurotoxin, *N*-methyl-(*R*)-salsolinol, induces DNA damage in human dopaminergic neuroblastoma SH-SY5Y cells. *J. Neurochem.* **69**, 322-329.

Maruyama W, G Sobue, K Matsubara, Y Hashizume, P Dostert and M Naoi (1997b) A dopaminergic neurotoxin, 1(*R*), 2(*N*)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, *N*-methylsalsolinol, and its oxidation product, 1,2(*N*)-dimethyl-dihydroxyisoquinolinium ion, accumulate in the nigro-striatal system of the human brain. *Neurosci. Lett.* 223, 61-64.

Maruyama W, Y Akao, MB Youdim and M Naoi (2000) Neurotoxins induce apoptosis in dopamine neurons: protection by *N*-propargylamine-1(*R*)- and (*S*)-aminoindan, rasagiline and TV1022. *J. Neural Transm. Suppl.* **60**, 171-186.

Masliah E, N Ge and L Mucke (1996) Pathogenesis of HIV-1 associated neurodegeneration. *Crit. Rev. Neurobiol.* **10**, 1360-1362.

Masliah E, E Rockenstein, I Veinbergs, M Mallory, M Hashimoto, A Takeda, Y Sagara, A Sisk and L Mucke (2000) Dopaminergic loss and inclusion body formation in a-synuclein mice: implications for neurodegenerative disorders. *Science* **287**, 1265-1269.

Matthews PM, N De Stefano, S Narayanan, GS Francis, JS Wolinsky, JP Antel and DL Arnold (1998) Putting magnetic resonance spectroscopy studies in context: axonal damage and disability in multiple scerosis. *Semin. Neurol.* **18**, 327-336.

Mattock C, M Marmot and G Stern (1988) Could Parkinson's disease follow intra-uterine influenza? *J. Neurol. Neurosurg. Psychiatr.* **51**, 753-756.

McNaught KS, U Thull, PA Carrupt, C Altomare, A Cellamare, B Carotti, P Testa, P Jenner and CD Marsden (1996) Nigral cell loss produced by infusion of isoquinoline derivatives structurally related to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neurodegeneration* **5**, 265-274.

McNaught KS, PA Carrupt, C Altomare, A Cellamare, B Carotti, P Testa, P Jenner and CD Marsden (1998) Isoquinoline derivatives as endogenous neurotoxins in the aetiology of Parkinson's disease. *Biochem. Pharmacol.* **56**, 921-933.

Melchitzky DS and DA Lewis (2000) Tyrosine hydroxylase- and dopamine transporter-immunoreactive axons in the primate cerebellum: evidence for a lobular- and laminar-specific dopamine intervention. *Neuropsychopharmacology* **22**, 466-472.

Merello M, MI Nouzeilles, A Cammarota and R Leiguarda (1999) Effect of memantine (NMDA antagonist) on Parkinson's disease: a double blind crossover randomised study. *Clin. Neuropharmacol.* **22**, 273-276.

Meshul CK and C Allen (2000) Haloperidol reverses the changes in striatal glutamatergic immunolabelling following a 6-OHDA lesion. *Synapse* **2**, 129-142.

Metman LV, PD Dotto, P Munckhof, J Fang, MM Mouradian and TN Chase (1998) Amantadine as treatment for dyskinesias and

motor fluctuations in Parkinson's disease. *Neurology* **50**, 1323-1329.

Mews I, M Bergmann, S Bunkowski, F Gullotta and W Brhck (1998) Oligodendrocyte and axon pathology in clinically silent multiple sclerosis lesions. *Multiple Sclerosis* **4**, 55-62.

Minami M, H Togashi, Y Koike, H Saito, N Nakamura and H Yasuda (1985) Changes in ambulation and drinking behaviour related to stroke in stroke-prone spontaneously hypertensive rats. *Stroke* **16**, 44-48.

Missale C, M Losa, F Boroni, M Giovanelli, A Balsari and PF Spano (1995) Nerve growth factor and bromocriptine: a sequential therapy for human bromocriptine-resistent prolactinomas. *Brit. J. Cancer* **6**, 1397-1399.

Mogi M and T Nagatsu (1999) Neurotrophins and cytokines in Parkinson's disease. In: Stern GM, Ed., Advances in Neurology, Parkinson's disease (Lippincott Williams & Wilkins, Philadelphia) Vol. 80, 135-139.

Mogi M, M Harada, H Narabayashi, H Inagaki, M Minami and T Nagatsu (1996) Interleukin (IL)-1β, IL-2, IL-4, IL-6 and transforming growth factor-α levels are elevated in ventricular cerebrospinal fluid in juvenile parkinsonian and Parkinson's disease. *Neurosci. Lett.* **211**, 13-16.

Mogi M, M Harada, P Riederer, H Narabayashi, K Fujita and T Nagatsu (1994a) Tumour necrosis factor-α (TNF-α) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. *Neurosci. Lett.* **165**, 208-210.

Mogi M, M Harada, T Kondo, P Riederer, H Inagaki, M Minami and T Nagatsu (1994b) Interleukin-1α, interleukin-6, epidermal growth factor and transforming growth factor-β are elevated in the brains from parkinsonian patients. *Neurosci. Lett.* **180**, 147-150.

Morrison PJ, RB Godwin-Austen and JA Raeburn (1996) Familial autosomal dominant dopa responsive Parkinson's disease in three living generations showing extreme anticipation and childhood onset. *J. Med. Genet.* **33**, 504-506.

Moser A and D Kömpf (1992) Presence of methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines, derivatives of the neurotoxin isoquinoline, in parkinsonian lumbar CSF. *Life Sci.* **50**, 1885-1891.

Mostofsky SH, AL Reiss, P Lockhart and MB Denckla (1998) Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *J. Child Neurol.* **13**, 434-439.

Mostofsky SH, AG Lasker, LE Cutting, MB Denckla and DS Zee (2001) Oculomotor abnormalities in attention deficit hyperactivity disorder: a preliminary study. *Neurology* **57**, 423-430.

Muller T, S Sallstrom Baum, P Haussermann, D Woitalla, H Rommelspacher, H Przuntek and W Kuhn (1998a) Plasma levels of *R*- and *S*-salsolinol are not increased in "*de-novo*" Parkinsonian patients. *J. Neural Transm.* **105**, 239-246.

Muller T, S Sallstrom Baum, P Haussermann, H Przuntek, H Rommelspacher and W Kuhn (1998b) *R*- and *S*-salsolinol are not increased in cerebrospinal fluid of Parkinsonian patients. *J. Neurol. Sci.* **164**; 158-162.

Myers MM, RE Musty and ED Hendley (1982) Attenuation of hyperactivity in the spontaneously hypertensive rat by amphetamine. *Behav. Neural Biol.* **34**, 42-54.

Nagatsu T (1997) Isoquinoline neurotoxins in the brain and Parkinson's disease. *Neurosci. Res.* **29**, 99-111.

Naoi M, W Maruyama, T Kasamatsu and P Dostert (1998a) Oxidation of *N*-methyl(*R*)salsolinol involvement to neurotoxicity and neuroprotection by endogenous catechol isoquinolines. *J. Neural Transm.* (Suppl.) **52**, 125-138.

Naoi M, W Maruyama, N Nakao, T Ibi, K Sahashi and MS Benedetti (1998b) (*R*)salsolinol *N*-methyltransferase activity increases in parkinsonian lymphocytes. *Ann. Neurol.* **43**, 212-216.

Naoi, M., Maruyama W., Takahashi, T., Akao, Y. and Nakagawa, Y. (2000a) Involvement of endogenous *N*-methyl(*R*)salsolinol in Parkinson's disease: induction of apoptosis and protection by (-) deprenyl. *J. Neural Transm.* **58**, 111-121.

Naoi M, W Maruyama Y Akao, J Zhang and H Parvez (2000b) Apoptosis induced by an endogenous neurotoxin, *N*-methyl(*R*)salsolinol, in dopamine neurons. *Toxicology* **153**, 123-141.

Narayanan PA, L Fu, E Pioro, N De Stefano, DL Collins, G Francis, JP Antel, PM Matthews and DL Arnold (1997) Imaging of axonal damage in multiple sclerosis: spatial distribution of magnetic resonance imaging lesions. *Ann. Neurol.* **41**, 385-391.

Narayanan PA, TJ Doyle, L Dejian and JS Wolinsky (1998) Serial proton magnetic resonance spectroscopic imaging, contrast-enhanced magnetic resonance imaging, and quantitative lesion volumetry in multiple sclerosis. *Ann. Neurol.* **43**, 56-71.

Narhi L, SJ Wood, S Steavenson, Y Jiang, GM Wu, D Anafi, SA Kaufman, F Martin, K Sitney, P Denis, J-C Louis, J Wypych, AL Biere and M Citron (1999) Both familial Parkinson's disease mutations accelerate α-synuclein aggregation. *J. Biol. Chem.* **274**, 9843-9846.

Nieoullon A, A Cheramy and J Glowinsky (1978) Release of dopamine in both caudate nuclei and both substantia nigrae in response to unilateral stimulation of cerebellar nuclei in the cat. *Brain Res.* **148**, 143-152.

Niwa T, N Takeda, N Kaneda, Y Hashizume and T Nagatsu (1987) Presence of tetrahydroisoquinoline and 2-methyl-tetrahydroquinoline in Parkinsonian and normal human brain. *Biochem. Biophys. Res. Commun.* **144**, 1084-1089.

Niwa T, N Takeda, H Yoshizumi, A Tatematsu, M Yoshida, P Dostert, M Naoi and T Nagatsu (1991) Presence of 2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and 1,2-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, novel endogenous amines, in parkinsonian and normal human brains. *Biochem. Biophys. Res. Commun.* **177**, 603-609.

Offen D, I Ziv, A Barzilai, S Gorodin, E Glater, A Hochman and E Melamed (1997) Dopamine-melanin induces apoptosis in PC12 cells. Possible implications for the etiology of Parkinson's disease. *Neurochem. Int.* **31**, 207-216.

Offen D, S Gorodin, E Melamed, J Hanania and Z Malik (1999) Dopamine-melanin is actively phagocytized by PC12 cells and cerebellar granular cells: possible implications for the etiology of Parkinson's disease. *Neurosci. Lett.* **260**, 101-104.

Oh JD, PD Dotto and TN Chase (1997) Protein kinase A inhibitor attenuates levodopa-induced motor response alterations in the hemi-parkinsonian rat. *Neurosci. Lett.* **228**, 5-8.

Oh JD, D Russell, CL Vaughan and TN Chase (1998) Enhanced tyrosine phosphorylation of striatal NMDA receptor units: effects of dopaminergic denervation and levodopa administration. *Brain Res.* **813**, 150-159.

Oh JD, CL Vaughan and TN Chase (1999) Effect of dopamine denervation and dopamine agonist administration on serine phosphorylation of striatal NMDA receptor subunits. *Brain Res.* **821**, 433-442.

Ohta S, O Tachikawa, Y Makino, Y Tasaki and M Hirobe (1990) Metabolism and brain accumulation of tetrahyroisoquinoline (TIQ), a possible parkinsonism inducing substance, in an animal model of a poor debrisoquine metabolizer. *Life Sci.* **46,** 599-605.

Okamoto K and K Aoki (1963) Development of a strain of spontaneously hypertensive rat. *Jpn. Circ. J.* **27**, 282-293.

Okamoto K, Y Yamori and A Nakaoka (1974) Establishment of the stroke-prone spontaneously hypertensive rat (SHR). *Circ. Res.* **34/35** (Suppl. I), 143-153.

Olanow CW and WG Tatton (1999) Etiology and pathogenesis of Parkinson's disease. *Ann. Rev. Neurosci.* **22**, 123-144. .

Olney JW, J Labruyere, G Wang, DF Wozniak, MT Price and AS Fix (1991) NMDA antagonist neurotoxicy: mechanism and prevention. *Science* **254**, 1515-1518.

Olney JW, N Farber, DF Wozniak, V Jevtovic-Todorovic and C Ikonomidou (2000) Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing grain. *Environ. Health Perspect.* **108**, 383-388.

Olney JW, DF Wozniak, V Jevtovic-Todorovic, NB Farber, P Bittigau and C Ikonomidou (2002) Glutamate and BABA receptor dysfunction in the fetal alcohol syndrome. *Neurotoxicity Res.* **4**, 315-325.

Olson L, EO Backlund, T Ebendal, R Freedman, B Hamberger, P Hansson, B Hoffer, U Lindblom, B Meyerson, I Stromberg *et al.* (1991) Intraputaminal infusion of nerve growth factor to support adrenal medullary autografts in Parkinson's disease. One-year follow-up of first clinical trial. *Arch. Neurol.* **48**, 373-381.

Ophoff RA, GM Terwindt, MN Vergouwe *et al.* (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{++} channel gene CACNL1A4. *Cell* **87**, 543-552.

Pahwa R, K Busenbark, C Gray and WC Koller (1993) Identical twins with similar onset of Parkinson's disease: a case report. *Neurology* **43**, 1159-1161.

Pal PK, ZK Wszolek, R Uitti, K Markoupoulou, SM Calne, AJ Stoessl and DB Calne (2001) Positron emission tomography of dopamine pathways in familial Parkinsonian syndromes. *Parkinsonism Relat. Disord.* **8**, 51-56.

Pappas BA, JV Gallivan, T Dugas, M Saari and R Ings (1980) Intraventricular 6-hydroxydopamine in the newborn rat and locomotor responses to drugs in infancy: no support for the dopamine depletion model of minimal brain dysfunction. *Psychopharmacology* **70**, 41-46.

Parent A, MC Asselin and PY Cote (1996) Dopaminergic regulation of peptide gene expression in the striatum of normal and parkinsonian monkeys. *Adv. Neurol.* **69**, 73-77.

Patterson SL, T Abel, TAS Deuel, KC Martin, JC Rose and ER Kandel (1996) Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron* **16**, 1137-1145.

Payami H, S Bernard, K Larsen, J Kaye and J Nutt (1995) Genetic anticipation in Parkinson's disease. *Neurology* **45**, 135-138.

Phillips HA, IE Scheffer, SF Berkovic, GE Hollway, GR Sutherland and JC Mulley (1995) Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2. *Nature Genet.* **10**, 117-118.

Phillips HA, C Marini, IE Scheffer, GR Sutherland, JC Mulley and SF Berkovic (2000) A de novo mutation in sporadic nocturnal frontal lobe epilepsy. *Ann. Neurol.* **48**, 264-267.

Pless R and JF Risher (2000) Mercury, infant neurodevelopment, and vaccination. *J. Pediatr.* **136**, 571-573.

Polymeropoulos MH (1998) Autosomal dominant Parkinson's disease and α-synuclein. *Ann. Neurol.* **44**, S63-S64.

Polymeropoulos MH, JJ Higgins, LI Golbe, WG Johnson, SE Ide, G Di Iorio, G Sanges, ES Stenroos, LT Pho, AA Schaffer, AM Lazzarini, RL Nussbaum and RC Duvoisin (1996) Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. *Science* **274**, 1197-1199.

Polymeropoulos MH, C Lavedan, E Leroy, SE Ide, A Deheja, A Dutra, B Pike, H Root, J Rubenstein, R Boyer, ES Stenroos, S Chandrasekharappa, A Athanassiadou, T Papapetropoulos, WG Johnson, AM Lazzarini, RC Duvoisin, G De Iorio, LI Golbe and RL Nussbaum (1997) Mutation in the α-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045-2047.

Powell AL, A Yudd, P Zee and DE Mandelbaum (1997) Attention deficit hyperactivity disorder associated with orbitofrontal epilepsy in a father and a son. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **10**, 151-154.

Radja F, L Descarries, KM Dewar and TA Reader (1993) Serotonin 5-HT_1 and 5-HT_2 receptors in adult rat brain after neonatal destruction of nigrostriatal dopamine neurons: a quantitative autoradiographic study. *Brain Res.* **606**, 273-285.

Redwood L, S Bernard and D Brown (2001) Predicted mercury concentrations in hair from infant immunizations: cause for concern. *Neurotoxicology* **22**, 691-697.

Regehr WG and IM Mintz (1994) Participation of multiple calcium channel types in transmission at single climbing fiber to Purkinje cell synapses. *Neuron* **12**, 605-613.

Riederer P (2003) Is there a subtype of developmental Parkinson's disease? *Neurotoxicity Res.* **5**, 27-34.

Riederer P, E Sofic, WD Rausch, B Schmidt, GP Reynolds, K Jellinger and MBH Youdim (1989) Transition metals, ferritin, glutathione, and ascorbic acid in parkinsonian brains. *J. Neurochem.* **52**, 515-520.

Riva D and C Giorgi (2000) The cerebellum contributes to higher functions during development: evidence from: series of children surgically treated for posterior fossa tumours. *Brain* **123**, 1051-1061.

Rubia K, S Overmeyer, E Taylor, M Brammer, SC Williams, A Simmons, C Andrew and ET Bullmore (1999) Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci. Biobehav. Rev.* **24**, 13-19.

Rudick RA, A Goodman, RM Herndon and HS Panitch (1999) Selecting relapsing remitting multiple sclerosis patients for treatment: the case for early treatment. *J. Neuroimmunol.* **98**, 22-28.

Rufer M, SB Wirth, A Hofer, R Dermietzel, A Pastor, H KettenMann and K Unsicker (1996) Regulation of connexin-43, GFAP, and FGF-2 is not accompanied by changes in astroglial coupling in MPTP-lesioned, FGF-2-treated parkinsonian mice. *J. Neurosci. Res.* **46**, 606-617.

Russell V, A de Villiers, T Sagvolden, M Lamm and J Taljaard (1995) Altered dopaminergic function in the prefrontal cortex, nucleus accumbens and caudate-putamen of an animal model of attention-deficit hyperactivity disorder – the spontaneously hypertensive rat. *Brain Res.* **676**, 343-351.

Ryvlin P, E Broussolle, H Piollet, F Viallet, Y Khalfallah and G Chazot (1995) Magnetic evidence imaging evidence of decreased putamenal iron content in idiopathic Parkinson's disease. *Arch. Neurol.* **52**, 583-588.

Sachs C and G Jonsson (1972) Degeneration of central noradrenaline neurons after 6-hydroxydopamine in newborn animals. *Res. Commun. Chem. Pathol. Pharmacol.* **4**, 203-220.

Sagvolden T, MA Metzger, HK Schiorbeck, A-L Rugland, I Spinnangr and G Sagvolden (1992) The spontaneously hypertensive rat (SHR) as an animal model of childhood hyperactivity (ADHD): changed reactivity to reinforcers and to psychomotor stimulants. *Behav. Neural Biol.* **58**, 103-112.

Sagvolden T, MB Pettersen and MC Larsen (1993) Spontaneously hypertensive rats (SHRs) as a putative animal model of childhood hyperkinesis: SHR behavior compared to four other rat strains.

Physiol. Behav. **54**, 1047-1055.

Sahenk Z, L Chen and JR Mendell (1999) Effects of PMP22 duplication and depletions on the axonal cytoskeleton. *Ann. Neurol.* **45**, 16-24.

Sandler M, S Carter, KR Hunter and GM Stern (1973) Tetrahydroisoquinoline alkaloids: *in vivo* metabolites of l-dopa in man. *Nature* **241**, 339-343.

Sarnat HB (1987) Disturbances of late neuronal migrations in the perinatal period. *Am. J. Disturb. Child* **141**, 969-980.

Sastry PS and KS Rao (2000) Apoptosis and the nervous system. *J. Neurochem.* **74**, 1-20.

Satoh JI and Y Kuroda (2001) Alpha-synuclein expression is up-regulated in Ntera2 cells during neuronal differentiation but unaffected by exposure to cytokines and neurotrophic factors. *Parkinsonism Relat. Disord.* **8**, 7-17.

Saul RC and CD Ashby (1986) Measurement of whole blood serotonin as a guide in prescribing psychostimulant medication for children with attentional deficits. *Clin. Neuropharmacol.* **9**, 189-195.

Scherer S (1999) Axonal pathology in myelinating diseases. *Ann. Neurol.* **45**, 6-7.

Schmahmann JD (1991) An emerging concept. The cerebellar contribution to higher function. *Arch. Neurol.* **48**, 1178-1187.

Schmahmann JD (1998) Cerebellum-the true thinking machine, In: Zigmond MJ, S Landis, J Roberts and L Squire (Eds), *Fundamental Neuroscience* (Academic Press, San Diego) pp 231-253.

Schmahmann JD (1999a) A new role of the cerebellum: the modulation of cognition and affect, In Joseph A (Ed.), *Movement Disorders* (Blackwell Science, Boston), pp 117-153.

Schmahmann JD (1999b) Cerebellum and brain stem, In: Toga A and J Mazziotta (Eds), *Human Brain Mapping: the applications* (Academic Press, San Diego) pp

Schmidt N and B Ferger (2001) Neurochemical findings in the MPTP model of Parkinson's disease. *J. Neural Transm.* **108**, 1263-1282.

Schmidt WJ and BD Kretschmer (1997) Behavioural pharmacology of glutamate receptors in the basal ganglia. *Neurosci. Biobehav. Rev.* 21, 381-392.

Scholz J, H Bamberg and A Moser (1997) *N*-methyl-norsalsolinol, an endogenous neurotoxin, inhibits tyrosine hydroxylase activity in the rat brain nucleus accumbens *in vitro*. *Neurochem. Int.* **31**, 845-849.

Schmued LC and KJ Hopkins (2000) Fluoro-Jade B: a high affinity fluorescent marker for the localization of neuronal degeneration. *Brain Res* **874**, 123-130.

Schmued LC, C Albertson and W Slikker Jr (1997) Fluoro-Jade: a novel fluorochrome for the sensitive and reliable histochemical localization of neuronal degeneration. *Brain Res.* **751**, 37-46.

Schröder N, A Fredriksson, MRM Vianna, R Roesler, I Izquierdo and T Archer (2001) Memory deficits in adult rats following postnatal iron administration. *Behav. Brain Res.* **124**, 77-85.

Schuerholz LJ, L Cutting, MM Mazzocco, HS Singer and MB Denckla (1997) Neuromotor functioning in children with Tourette syndrome with and without attention deficit hyperactivity disorder. *J. Child Neurol.* **12**, 438-442.

Schuerholz LJ, HS Singer and MB Denckla (1998) Gender study of neuropsychological and neuromotor function in children with Tourette syndrome with and without attention-deficit hyperactivity disorder. *J. Child Neurol.* **13**, 277-282.

Schulz JB and J Dichgans (1999) Molecular pathogenesis of movement disorders: are protein aggregates a common link in neuronal degeneration? *Curr. Opin. Neurol.* **12**, 433-439.

Schwartz J-C, J Diaz, C Pilon and P Sokoloff (2000) Possible implications of the D_3 receptor in schizophrenia and antipsychotic drug actions. *Brain Res. Rev.* **31**, 277-287.

Schweitzer JB, TL Faber, ST Grafton, LE Tune, JM Hoffman anc CD Kilts (2000) Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *Am. J. Psychiatry* **157**, 278-280.

Scott WK, MA Nance, RL Watts, JP Hubble, WC Koller, K Lyons, R Pahwa, MB Stern, A Colcher, BC Hiner, J Jankovic, WG Ondo, FH Allen Jr, CG Goetz, GW Small, D Masterman, F Mastaglia, NG Laing, JM Stajich, B Slotterbeck, MW Booze, RC Ribble, E Rampersaud, SG West, RA Gibson, LT Middleton, AD Roses, JL Haines, BL Scott, JM Vance and M Pericak-Vance (2001) Complete genomic screen in Parkinson's disease: evidence for multiple genes. *JAMA* **286**, 2239-2244.

Seeman P and BK Madras (1998) Anti-hyperactivity medication: methylphenidate and amphetamine. Mol. Psychiatr. 3, 386-396.

Shaywitz BA, JH Klopper and JW Gordon (1976) Methylphenidate in 6-hydroxydopamine-treated developing rat pups. *Arch. Neurol.* **35**, 463-469.

Shaywitz BA, RD Yager and JH Klopper (1978) Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. *Science* **191**, 305-307.

Shima T, T Sarna, H Swartz, A Stroppolo, R Gerbasi and L Zecca (1997) Binding of iron to neuromelanin of human substantia nigra and synthetic melanin: an electron paramagnetic resonance spectroscopy study. *Free Rad. Biol. Med.* **23**, 110-119.

Shimai S and M Satoh (1985) Behavioural teratology of methyl mercury. *J. Toxicol. Sci.* **10**, 199-216.

Shoham S and MBH Youdim (2000) Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases. *Cell. Mol. Biol.* **46**, 743-760.

Singh NA, C Charlier, D Stauffer *et al.* (1998) A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nature Genet.* **18**, 25-29.

Smith Y, BD Bennett, JP Bolam, A Parent and AF Sadikot (1994) Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. *J. Comp. Neurol.* **1**, 1-19.

Snider RS and A Maiti (1976) Cerebellar contributions to the Papez Circuit. *J. Neurosci. Res.* **2**, 133-146.

Snider SR and RS Snider (1982) Structural and functional relationships between cerebellum and catecholamine systems: an overview. *Exp. Brain Res* (Suppl. 6), 45.

Snider RS, A Maiti and SR Snider (1976) Cerebellar pathways to ventral midbrain and nigra. *Exp. Neurol.* **53**, 714-728.

Snyder AM, MJ Zigmond and RD Lund (1986) Sprouting of serotonergic afferents into striatum after dopamine-depleting lesions in infant rats: a retrograde transport and immunocytochemical study. *J. Comp. Neurol.* **245**, 274-281.

Sofic E, P Riederer, H Heinsen, H Beckman, GP Reynolds, G Hebenstreit and MBH Youdim (1988) Increased iron(III) and total iron content in post mortem substantia nigra of parkinsonian brain. *J. Neural Transm.* **74**, 199-205.

Sofic E, W Paulus, K Jellinger, P Riederer and MBH Youdim (1991) Selective increase of iron in substantia nigra zona compacta of parkinsonian brains. *J. Neurochem.* **56**, 978-982.

Sokoloff P, B Le Foll, S Pérachon, R Bordet, S Ridray and J-C Schwartz (2001) The dopamine D_3 receptor and drug action. *Neurotoxicity Res.* **3**, 433-441.

Sokoloff P, O Guillin, J Diaz, P Carroll and N Griffon (2002) Brain-

derived neurotrophic factor controls dopamine D_3 receptor expression: implications for neurodevelopmental psychiatric disorders. *Neurotoxicity Res.* **4**, 671-678.

Spillantini MG, ML Schmidt, VM Lee, JQ Trojanowski, R Jakes and M Goedert (1997) Alpha-synuclein in Lewy bodies. *Nature* **28**, 839-840.

Spillantini MG, RA Crowther, R Jakes, M Hasegawa and M Goedert (1998) a-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc. Natl. Acad. Sci. USA* **95**, 6469-6473.

Spivak B, Y Vered, R Yoran-Hegesh, E Averbuch, R Mester, E Graf and A Weizman (1999) Circulatory levels of catecholamines, serotonin and lipids in attention deficit hyperactivity disorder. *Acta Psychiatr. Scand.* **99**, 300-304.

Stein JF and TZ Aziz (1999) Does imbalance between basal ganglia and cerebellar outputs cause movement disorders. *Curr. Opin. Neurol.* **12**, 667-669.

Stevenson VL and DH Miller (1999) Magnetic resonance imaging in the monitoring of disease progression in multiple sclerosis. *Multiple Sclerosis* **5**, 268-272.

Stoltberg-Didinger G and S Markwort (1990) Prenatal methylmercury exposure results in dendritic spine dysgenesis in rats. *Neurotoxicol. Teratol.* **12**, 573-576.

Storch A, A Kaftan, K Burkhardt and J Schwarz (2000) 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol) is toxic to dopaminergic neuroblastoma SH-SY5Y cells via impairment of cellular energy metabolism. *Brain Res.* **855**, 67-75.

Surh YJ, YJ Jung, JH Jang, JS Lee and HR Yoon (2002) Iron enhancement of oxidative DNA damage and neuronal cell death induced by salsolinol. *J. Toxicol. Environ. Health. A* **65**, 473-488.

Sveinbjörnsdottir S, AA Hicks, T Jonsson, H Petursson, G Gugmundsson, ML Frigge, A Kong, JR Gulcher and K Stefansson (2000) Familial aggregation of Parkinson's disease in Iceland. *N. Engl. J. Med.* **343**, 1765-1770.

Sykes DH, VI Douglas, G Weiss and KK Minde (1971) Attention in hyperactive children and the effect of methylphenidate (ritalin). *J. Child Psychol. Psychiatr.* **12**, 129-139.

Szatmari P, MN Boyle and DR Offord (1989) ADHD and conduct disorder: degree of diagnostic overlap among correlates. *J. Am. Acad. Child Adolesc. Psychiatr.* **28**, 865-872.

Tagamets MA and B Horwitz (1999) Functional brain imaging and modelling of brain disorders. *Prog. Brain Res.* **121**, 185-200.

Tamminga CA, JM Dale, L Goodman, H Kaneda and N Kaneda (1990) Neuroleptic-induced vacuous chewing movements as an animal model of tardive dyskinesia: a study of three rat strains. *Psychopharmacology* **102**, 474-478.

Tanner CM, R Ottman, SM Goldman *et al.* (1999) Parkinson's disease in twins. An etiologic study. *J. Am. Med. Assoc.* **281**, 341-346.

Taylor E (1998) Clinical foundations of hyperactivity research. Behav. *Brain Res.* **94**, 11-24.

Teicher MH, Y Ito, CA Glod and NI Barber (1996) Objective measurement of hyperactivity and attentional problems in ADHD. *J. Am. Acad. Child Adolesc. Psychiatry* **35**, 334-342.

Teicher MH, CM Anderson, A Polcari, CA Glod, LC Maas and PF Renshaw (2000) Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nature Med.* **6**, 470-473.

Tellerman K, A Astrow, S Fahn, SR Snider, RS Snider and JM Glassgold (1979) Cerebellar control of catecholaminergic activities: implications for drug therapy of movement disorders. *Int. J. Neurol.* **13**, 135-155.

Thoenen H (1995) Neurotrophins and neuronal plasticity. *Science* **270**, 593-598.

Thompson KT, S Shoham and JR Connor (2001) Iron and neurodegenerative disorders. *Brain Res. Bull.* **55**, 155-164.

Togashi H, M Minami, Y Bando, Y Koike, K Shinamura and H Saito (1982) Effects of clonidine and guanfacine on drinking and ambulation in spontaneously hypertensive rats. *Pharmacol. Biochem. Behav.* **17**, 519-522.

Togashi H, M Matsumoto, M Yoshioka, M Hirokami, M Minami and H Saito (1994) Neurochemical profiles in cerebrospinal fluid of stroke-prone spontaneously hypertensive rats. *Neurosci. Lett.* **166**, 117-120.

Trapp BD, J Peterson, RM Ransohoff, R Rudick, S Mörk and L Bö (1998) Axonal transection in the lesions of multiple sclerosis. *N. Engl. J. Med.* **338**, 278-285.

Trapp BD, RM Ransohoff, E Fisher and RA Rudick (1999) Neurodegeneration in multiple sclerosis: relationship to neurological disability. *Neuroscientist* **5**, 48-57.

Trojanowski JQ, M Goedert, T Iwatsubo and VM-Y Lee (1998) Fatal attractions: abnormal protein aggregation and neuron death in Parkinson's disease and Lewy body dementia. *Cell Death Differ.* **5**, 832-837.

Tsuda K, S Tsuda, Y Masuyama and M Goldstein (1991) Alteration of catecholamine release in the central nervous system of spontaneously hypertensive rats. *Jpn. Heart J.* **32**, 701-709.

Tu P-H, JE Galvin, M Baba, B Giasson, T Tomita, S Leight, S Nakajo, T Iwatsubo, JQ Trojanowski and VM-Y Lee (1998) Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble α-synuclein. *Ann. Neurol.* **44**, 415-422.

Ueno K, H Togashi, K Mori, M Matsumoto, S Ohashi, A Hoshino, T Fujita, H Saito, M Minami and M Yoshioka (2000) Behavioural and pharmacological relevance of stroke-prone spontaneously hypertensive rat as an animal model of developmental disorder. *Behav. Pharmacol.* **13**, 1-14.

Ueno K, H Togashi, M Matsumoto, S Ohashi, H Saito and M Yoshioka (2002) Alpha4beta2 nicotinic acetylcholine receptor activation ameliorates impairment of spontaneous alternation behavior in Stroke-Prone Spontaneously Hypertensive Rats, an animal model of attention deficit hyperactivity disorder. *J. Pharmacol. Exp. Ther.* **302**, 95-100.

Uitti RJ, H Shinotoh, M Hayward, M Schulzer, E Mak and DB Calne (1997) Familial Parkinson's disease – a case-control study of families. *Can. J. Neurol. Sci.* **24**, 127-132.

Van Bogaert P and HB Szliwowski (1996) EEG findings in acetazolamide-responsive hereditary paroxysmal ataxia. *Neurophysiol. Clin.* **26**, 335-340.

Van Waesberghe JHTM, W Kamphorst, CJA De Groot, MAA van Walderveen, JA Casteljins, R Ravid, GJ Lycklama a Nijeholt, P van der Valk, CH Polman, AJ Thompson and F Barkhof (1999) Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. *Ann. Neurol.* **46**, 747-754.

Vetulani J, L Antkiewicz-Michaluk, I Nalepa and M Sansone (2003) A possible physiological role for cerebral tetrahydroisoquinolines. *Neurotoxicity Res.* **5**, 147-156.

Vieregge P, H-J Friedrich, A Röhl, G Ulm and I Heberlein (1994) Multifactorial etiology in idiopathic Parkinson's disease, a case-control study. *Nervenarzt* **65**, 390-395.

Vighetto A, JC Froment, M Trillet and G Aimard (1988) Magnetic resonance imaging in familial paroxysmal ataxia. *Arch. Neurol.* **45**, 547-549.

Volkow ND, GJ Wang, JS Fowler, J Logan, B Angrist, R Hitzemann, J Lieberman and N Pappas (1997) Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D_2 receptors. *Amer. J. Psychiatr.* **154**, 50-55.

Volpe BT, J Wildmann and CA Altar (1998) Brain-derived neurotrophic factor prevents the loss of nigral neurons induced by excitotoxic striatal-pallidal lesions. *Neuroscience* **83**, 741-748.

Voogd J and M Glickstein (1998) The anatomy of the cerebellum. *TINS* **21**, 370-375.

Vorhees CV (1985) Behavioral effects of prenatal methylmercury in rats: a parallel trial to the collaborative behavioural teratology study. *Neurobehav. Toxicol. Teratol.* 7, 717-725.

Wakamori M, K Yamazaki, H Matsunodaira, T Teramoto, I Tanaka, T Niidome, K Sawada, Y Nishizawa, N Sekiguchi, E Mori, Y Mori and K Imoto (1998) Single tottering mutations responsible for the neuropathic phenotype of the P-type calcium channel. *J. Biol. Chem.* **273**, 34857-34867.

Wakabayashi K, S Engelender, M Yoshimoto, S Tsuji, CA Ross and H Takahashi (2000) Synphilin-1 is present in Lewy bodies in Parkinson's disease. *Ann. Neurol.* **47**, 521-523.

Walker DG, K Terai, A Matsuo, TG Beach, EG McGeer and PL McGeer (1998) Immunohistochemical analyses of fibroblast growth factor receptor-1 in the human substantia nigra. Comparison between normal and Parkinson's disease cases. *Brain Res.* **2**, 181-187.

Wallace RH, DW Wang, R Singh, IE Scheffer, AL George Jr, HA Phillips, K Saar, A Reis, EW Johnson, GR Sutherland, SF Berkovic and JC Mulley (1998) Febrile seizures and generalised epilepsy associated with a mutation in the Na^+-channel beta 1 subunit gene SCN1B. *Nature Genet.* **19**, 366-370.

Wang W, X Fang, X Cheng, D Jiang and Z Lin (1993) A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China. *Neuroepidemiology* **12**, 209-218.

Ward CD, RC Duvoisin, SE Ince, JD Nutt, R Eldridge and DB Calne (1983) Parkinson's disease in 65 pairs of twins and in a set of quadruples. *Neurology* **33**, 815-824.

Watanabe Y, M Fujita, Y Ito, T Okada, H Kusuoka and T Nishimura (1997) Brain dopamine transporter in spontaneously hypertensive rats. *J. Nucl. Med.* **38**, 470-474.

Westenbroek RE, T Sakurai, EM Elliot, JW Hell, TV Starr, TP Snutch and WA Catterall (1995) Immunochemical identification and subcellular distribution of the alpha 1A subunits of brain calcium channels. *J. Neurosci.* **15**, 6403-6418.

Wirshing WC (2001) Movement disorders associated with neuroleptic treatment. *J. Clin. Psychiatr.* **62**, 15-18.

Withers GS, JM George, GA Banker and DF Clayton (1997) Delayed localization of synelfin (synuclein NACP) to presynaptic terminals in cultured rat hippocampal neurons. *Dev. Brain Rev.* **99**, 87-94.

Wong GF, CS Gray, RS Hassanein and WC Koller (1991) Environmental risk factors in siblings with Parkinson's disease. *Arch. Neurol.* **48**, 287-289.

Wooten GF, LJ Currie, JP Bennett *et al.* (1997) Maternal inheritance in Parkinson's disease. *Ann. Neurol.* **41**, 265-268.

Wszolek ZK and K Markopoulou (1999) Molecular genetics of familial parkinsonism. *Parkinsonism Relat. Disord.* **5**, 145-155.

Wszolek ZK and RJ Uitti (1999) The clinical genetics of Parkinson's disease. *Neurosci. News* **2**, 66-72.

Wultz B, T Sagvolden, EI Moser and M-B Moser (1990) The spontaneously hypertensive rat as an animal model of attention-deficit hyperactivity disorder: effects of methylphenidate on exploratory behaviour. *Behav. Neural Biol.* **53**, 88-102.

Wyllie AH, JFR Kerr and AR Currie (1980) Cell death: the significance of apoptosis. *Int. Rev. Cytol.* **68**, 251-306.

Xiong G and M Matsushita (2000) Connections of Purkinje cell axons of lobule X with vestibulospinal neurons projecting to the cervical cord in the rat. *Exp. Brain Res.* **131**, 491-499.

Yamakawa T, Y Kotake, M Fujitani, H Shintani, Y Makino and S Ohta (1999) Regional distribution of parkinson-preventing endogenous tetrahydroisoquinoline derivatives and an endogenous parkinsonism-preventing substance-synthesizing enzyme in monkey brain. *Neurosci. Lett.* **276**, 68-70.

Yamori Y and R Horie (1977) Developmental course of hypertension and regional cerebral blood flow in stroke-prone spontaneously hypertensive rats. *Stroke* **8**, 456-461.

Yehuda S and MBH Youdim (1989) Brain iron: a lesson from animal models. *Am. J. Clin. Nutr.* **50**(Suppl. 3), 618-625.

Yew DT, CB Luo, WZ Shen, PH Chow, DR Zheng and MC Yu (1995) Tyrosine hydroxylase- and dopamine-beta-hydroxylase-positive neurons and fibres in the developing human cerebellum—an immunohistochemical study. *Neuroscience* **65**, 453-461.

Yin X, TO Crawford, JW Griffin, P Tu, VM-Y Lee, C Li, J Roder and BD Trapp (1998) Myelin-associated glycoprotein is a myelin signal that modulates the calibre of myelinated axons. *J. Neurosci.* **18**, 1953-1962.

Yoshida M, M Ogawa, K Suzuki and T Nagatsu (1993) Parkinsonism produced by tetrahydroisoquiniline (TIQ) or the analogues. *Adv. Neurol.* **60**, 207-211.

Youdim MBH and S Yehuda (2000) The neurochemical basis of cognitive deficits induced by brain iron deficiency: involvement of dopamine-opiate system. *Cell. Mol. Biol.* **46**, 491-500.

Youdim MBH, D Ben-Schachar, R Ashkenazi and S Yehuda (1983) Brain iron and dopamine receptor function. *Adv. Biochem. Psychopharmacol.* **37**, 309-321.

Youdim MBH, D Ben-Shachar and S Yehuda (1989) Putative biological mechanisms of the effect of iron deficiency on brain biochemistry and behaviour. *Am. J. Clin. Nutr.* **50**, 607-615.

Youdim MBH, D Ben-Shachar and P Riederer (1993) Parkinson's disease and increased iron in substantia nigra zona compacta. *Mov. Disord.* **8**, 1-12.

Youdim MBH, E Grunblatt, Y Levites, G Maor, S Mandel (2002) Early and late molecular events in neurodegeneration and neuroprotection in Parkinson's disease MPTP model as asssessed by cDNA microarray; the role of iron. *Neurotoxicity Res.* **4**, 679-689.

Youdim MBH, KL Leenders and D Ben-Shachar (2002) Brain iron uptake and transport in animal model of iron deficiency, tardive dyskinesia and neurodegenerative disease. *Neurotoxicity Res.* **4**, 679-689.

Yu J, L Källström, FA Wiesel and AE Johnson (1999) Neurochemical changes in the entopeduncular nucleus and increased oral behaviour in rats treated subchronically with clozapine of haloperidol. *Synapse* **34**, 192-207.

Yue Q, JC Jen, SF Nelson and RW Baloh (1997) Progressive ataxia due to a missense mutation in a calcium channel gene. *Am. J. Hum. Genet.* **61**, 1078-1087.

Yue Q, JC Jen, MM Thwe, SF Nelson and RW Baloh (1998) *De novo* mutation in CACNA1A caused acetazolamide-responsive episodic ataxia. *Am. J. Med. Genet.* **77**, 298-301.

Zarranz de Ysern ME and LA Ordonez (1981) Tetra-hydroisoquinolines: a review. *Progr. Neuropsychopharmacol.* **5**, 343-535.

Zawada WM, DJ Zastrow, ED Clarkson, FS Adams, KP Bell anc CR Freed (1998) Growth factors improve immediate survival of embryonic dopamine neurons after transplantation into rats. *Brain Res.* **786**, 96-103.

Zecca L, M Gallorini, V Schünemann, A Trautwein, M Gerlach, P Riederer, P Vezzoni and D Tampellini (2001) Iron, neuromelanin and ferritin content in substantia nigra of normal subjects at different ages. Consequences for iron storage and neurodegenerative processes. *J. Neurochem.* **76**, 1766-1773.

Zoghbi HY and HT Orr (2000) Glutamine repeats and neurodegeneration. *Ann. Rev. Neurosci.* **23**, 217-247.