J Neural Transm (2007) 114: XXXIII–XLI
DOI 10.1007/s00702-006-0572-9
Printed in The Netherlands

Journal of Neural Transmission

Abstract

Movement disorders: Neurodevelopment and neurobehavioural expression

T. Archer[1] and **R. J. Beninger**[2]

[1] Department of Psychology, University of Göteborg, Göteborg, and University of Kalmar, Kalmar, Sweden
[2] Departments of Psychology and Psychiatry, Queen's University, Kingston, Canada

Received: June 20, 2006 / Accepted: July 31, 2006 / Published online: October 6, 2006

Summary Braak and co-workers have recently shown that movement disorders such as Parkinson's disease develop progressively over years with early neuronal losses in brainstem regions caudal to the substantia nigra. The relevance of this finding to notions of comorbidity between movement disorders and psychiatric symptoms was recognised at the recent meeting concerning, ''Implications of Comorbidity for the Etiology and Treatment of Neuropsychiatric Disorders'' held in Oct. 2005 in Mazagon, Spain. The identification of stages in the early development of neurodegenerative disorders appeared to unify multiple, diverse findings. These included: novel therapeutic innovations for Parkinson's disease, Alzheimer's disease and depression in the aged; the neurochemical ontogeny of drug-induced oral dyskinesias; the types of chemical agents abused in neuropsychiatric states; postnatal iron overload effects upon the functional and interactive role of dopaminergic and noradrenergic pathways that contribute to the expression of movement disorders; and the spectrum of motor symptoms expressed in schizophrenia and attention deficit hyperactivity disorder and the eventual treatment of these disorders. A continued focus on a number of neuropsychiatric diseases as progressive disorders may lead to further advances in understanding their etiology and in developing better therapeutics.

Keywords: ADHD, basal ganglia, comorbidity, development, movement disorder, neurodegeneration, Parkinson's disease, schizophrenia, staging.

Pathological staging of brain disorders

Aging without a disease complication provides a definition of ''healthy'' normal aging. Nevertheless, a high proportion of aged individuals who do not exhibit symptoms of disease by leading relatively normal lives show pathological alterations like those associated with Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and/or cerebrovascular disease (CVD). According to the notions introduced by Braak and co-workers (e.g., Thal et al., 2004), these alterations are restricted to specific regions of the brain and may be associated with phases of premorbidity (or preclinical debut stages) of these neurodegenerative diseases. For instance, AD-related alterations do not routinely accompany normal healthy brain aging (Arnold et al., 1991; Braak et al., 1996; Hyman et al., 1984; van Hoesen and Hyman, 1990) but rather these changes indicate differential stages of neuropathology in as yet asymptomatic individuals and in patients presenting with symptoms (Braak and Del Tredici, 2004; Braak et al., 2000, 2003c). Thus, although aging remains a major risk factor for the neurodegenerative diseases, it does not necessarily imply age-related diseases; aging is sufficient but not necessary. Thal et al. (2004) concluded that, even in the absence of clinical symptoms, early brain pathological disease-related changes constitute the debut of AD, PD, DLB and CVD rather than normal constituents of the aging process. Against this background, which provides a unique context for the accummulating evidence of 'shared symptoms', we will discuss studies pertaining to comorbidity in neurodegenerative movement disorders.

The study of movement disorders might take as its point-of-departure the recent Braak et al. (2003a, b) findings that PD-like brain disorders develop progressively over years and the loss of neurons in specific brain regions encompasses both pre-symptomatic and post-symptomatic phases. Multiple neuronal systems are involved in sporadic PD with a putative etiology stemming from progressive changes in a few susceptible types of neurons with essential α-synuclein-immunopositive Lewy neurites and Lewy

Correspondence: Trevor Archer, Department of Psychology, University of Göteborg, P.O. Box 500, SE 45030 Göteborg, Sweden
E-mail: trevor.archer@psy.gu.se

body components. According to this notion, lesions occur initially in the motor nuclei of the glossopharyngeal and vagus nerves as well as anterior olfactory nucleus, from which more rostral areas become affected gradually, the disease process advancing in an ascending fashion. The caudal raphe, gigantocellulear reticular nucleus and locus coeruleus and sub-coeruleus are next affected, followed by the substantia nigra compacta. The anteromedial temporal mesocortex is next afflicted, after which the neocortex, then the high order sensory association and prefrontal cortical areas followed by first order sensory association/premotor areas and primary sensory/motor fields, each step tracing the course of brain pathology.

From a perspective of neurologic-psychiatric comorbidity, Przuntek et al. (2004) have proposed that the motor symptoms in PD patients are preceeded by the insidious onset of mild, psychopathological, i.e., cognitive and perceptual, disturbances expressed by olfactory and visual dysfunction, with consequent behavioural alteration, e.g., reduced stress tolerance. They have described an initial premotor phase, originating in non-dopaminergic areas, a conflagration of onset of gastrointestinal brainstem-associated and sensory deficits leading eventually to the expression of motor symptoms and further pathological development. Przuntek et al. (2004) suggest that an unknown pathogen entering through the gastrointestinal tract affects brainstem nuclei and initiates the progression of degeneration that leads to PD, producing multiple comorbid symptoms.

Aspects of neuropathological staging and expression

Youdim and co-workers (in press) reviewed the therapeutic profiles of drug candidates that are designed to express a diversity of pharmacological properties and multiplicity of target sites in their actions against the symptoms of neurodegenerative disorders. For example, ladostigil (Sterling et al., 2002; Weinstock et al., 2000a, b; Youdim and Buccafusco, 2005) combines a selective monoamine oxidase-B (MAO-B) inhibition with a cholinesterase inhibitory activity to provide a pharmacophore with neuroprotective and procholinergic properties as well as an iron chelator moiety. Ladostigil (TV3326; (N-propargyl-(3R) aminoindan-5yl)-ethyl) thereby incorporates the pharmacological actions of rasagiline, rivastigmine and M30, and is potentially useful for treating the comorbidity underling the disease states AD, PD and LBD, outlined by, for example, Braak and Braak (1991).

The incidence of depressive symptoms in AD and PD patients is of major importance in attempts to understand comorbid brain pathologies (Leentjens, 2004; McDonald et al., 2003; Shih et al., 2004; Veazey et al., 2005). An antidepressant action of ladostigil was observed, using the forced swim test (Borsini and Meli, 1988) in laboratory rats and mice (Weinstock et al., 2000b, c). Concurrently, an anti-Parkinsonian action of the compound as a result of its MAO-A and MAO-B inhibiting properties was indicated (Finberg et al., 1996a, b; Gal et al., 2005; Huang et al., 1999; Wu et al., 2000). The anticholinesterase action of ladostigil for a therapeutic efficacy in AD enjoys much support (DeKosky et al., 2002; Francis et al., 1999; Giacobibi, 2004; Racchi et al., 2004; Weinstock et al., 2001), particularly in view of evidence that the compound may block certain neurodegenerative processes (Francis et al., 2005). The neuropathological sequence of cytoskeleton changes relating to neuronal damage and debris in AD is relevant from the staging perspective (Braak and Braak, 1994, 1999; Braak et al., 1994). Thus, studies of the early stages of AD reveal that formation of the intraneuronal cytoskeletal alterations precedes formation of aggregated amyloid-β protein (Braak and Braak, 1997). Accordingly, accumulation of abnormally phosphorylated, soluble tau protein (cf., Palomo et al., 2004), incorporated in projection cells with initial ''pretangle'' cytoskeletal changes, is distributed throughout the cell body and cellular processes (Bancher et al., 1989), and appears in the trans-entorhinal cortex, magnocellular nuclei of the basal forebrain and locus coeruleus prior to occurence of traces of amyloid-β (Braak and Del Tredici, 2004; see fig. 1), with deposits of insoluble β-amyloid proteins developing in parts of the basal temporal neocortex (Thal et al., 2000). An elevated expression in generation of β-amyloid proteins may contribute to amyloidogenesis processes in AD (Arends et al., 2000; Gouras et al., 2005; Klyubin et al., 2005). It seems to be the case that the cholinesterase inhibiting actions of ladostigil and other anticholinesterases, with or without the MAO-inhibiting component (using the S-isomer, TV3279), exert a variety of actions that counteract the amyloidal processes in AD (Pakaski and Kasa, 2003; Yogev-Falach et al., 2002, 2003; Zhang et al., 2004; Zimmerman et al., 2004). Finally, the neuroprotectant profiles of the N-propargylamine component itself, among other aspects showing an anti-apoptic action (Maruyama et al., 2003, 2004; Weinreb et al., 2004; Yi et al., 2005), appear relevant (Youdim, 2003; Youdim and Weinstock, 2002a, b; Youdim et al., 2001a, b; Zheng et al., 2005). All this serves to impart a particular instrumental feature upon ladostigil; on the one hand, it serves as a substrate for elucidating the complexities of comorbidity, and on the other, as a template for considering the notion of staging from a novel perspective.

Chronic dosing with typical antipsychotic agents, classically used in the treatment of schizophrenia (e.g., Farde et al., 1988; Seeman et al., 1975), carries the risk of inducing extrapyramidal side effects (EPS). These compounds, e.g., haloperidol, are associated with a variety of EPS that may include dystonia, akathisia, drug-induced Parkinsonism and the tardive dyskinesias (TDs), with varying extents of personal severity (Casey, 1989, 1991, 1994; Deniker, 1983; Lewander, 1994; Youssef and Waddington, 1987; see also Schmidt and Beninger, in press), whereas administration of the atypical clozapine is associated with TDs in a subset of patients (Davé, 1994; Kane et al., 1993; Kurz et al., 1993; Tamminga et al., 1994). TDs constitute the most serious of the EPS and are characterised by vacous, purposeless, involuntary movements that include chewing behaviour, tongue (often circling) protrusions, lip-smacking, and grimacing in a repetitive fashion, and may incorporate movement disorders in other body parts (Albin et al., 1989; DeLong, 1990; Jeste and Caligiuri, 1993; Mink, 1996). In animal studies, the phenomenon of ''vacous chewing movements'' (VCMs), whether tardive or acute (Egan et al., 1996), was associated both with an imbalance between dopamine D_1- and D_2-like receptors (Daly and Waddington, 1993; Koshikawa et al., 1987; Levin et al., 1989; Rupniak, 1985) and long-term typical neuroleptic treatment (Waddington et al., 1983, 1989). VCMs have also been reported following long-term treatment with an atypical (Kakigi et al., 1995; Lieberman et al., 1991; Yu et al., 1999) possibly due, in the case of clozapine, to a dopamine D_1-like receptor agonist action (Salmi and Ahlenius, 1996). Nevertheless, there is evidence to indicate that clozapine is less likely to cause, and may even ameliorate TD and remains markedly useful for the treatment of chronically psychotic patients with TD (De Leon et al., 1991; Kalian et al., 1993; Lamberti and Bellnier, 1993; Levkovitch et al., 1995; Littrell and Magill, 1993; Naber et al., 1989; Nair et al., 1996; Wirshing et al., 1990). This severe sensitivity to neuroleptic compounds constitutes a major clinical problem in DLB. An evaluation of severe neuroleptic sensitivity reactions, blind to diagnosis, confirmed high prevalence in DLB and identified high frequencies in PD and PD with dementia. In the light of comorbidity implications as derived from Braak's staging notions, these findings must imply important relationships that affect clinical practice (Aarsland et al., 2005; Dalack et al., 1998a).

In their focus upon dopamine D_1-like receptor influences, Kostrzewa and co-workers (in press) applied a novel animal model of TDs by utilizing neonatal 6-hydroxydopamine (6-OHDA) administration, following desipramine pretreatment, to destroy nigrostriatal dopamine fibres, thereby causing a denervation-induced sensitivity (Brus et al., 1994; Kostrzewa, 1995; Kostrzewa and Gong, 1991; Kostrzrewa and Hamdi, 1991; Kostrzewa et al., 1993). Several studies were described involving treatment of neonatal dopamine-denervated rats with the D_1-like receptor agonist SKF 38393. A very low dose produced VCMs (Kostrzewa and Gong, 1991). If the depletion of striatal dopamine was less than 98.5%, there was no induction of VCMs by SKF 38393 (Gong et al., 1993a). Additional studies implicated other neurotransmitter systems in this animal model of the oral dyskinesias (Gong et al., 1993b, 1994; Huang and Kostrzewa, 1994; Huang et al., 1997). Thus, neonatal 6-OHDA lesions also induced serotonin receptor supersensitivity. A serotonin receptor antagonist attenuated VCMs induced by a D_1-like dopamine receptor agonist (Gong and Kostrzewa, 1992; Gong et al., 1992; Plech et al., 1995). Dopamine denervation-induced supersensensitivity may be associated with notions of staging through the interactive role of serotonergic transmission modulating expressions of VCMs; thus, VCMs were abolished by neonatal serotonin lesions (Brus et al., 1994). Kostrzewa et al. (in press) indicated that a marked aspect of neonatal dopamine denervation is supersensitization of the dopamine D_1 receptors (necessarily Stage 1) but it is then followed by supersensitization of 5-HT_2 receptors.

Substance abuse by schizophrenic patients remains an important issue (cf. O'Brien et al., 2004); these patients are at disproportionately high risk (Regier et al., 1990), commonly abusing the same agents as the general public (Anthony et al., 1994). The comorbidity of smoking and nicotine dependence in schizophrenic patients (e.g., Zammit et al., 2003) is well documented. Thus, (i) nicotine may play a role in medicating negative symptoms (Aguilar et al., 2005; Dalack et al., 1998b) although some have suggested reconsideration of the ''negative-symptom'' construct in the cormorbid disease state (Krystal et al., in press), (ii) schizophrenia incorporates a primary defect in brain nicotinic systems modulating cognition and sensory gating (Adler et al., 1992; Sacco et al., 2004, 2005; Sarter et al., 2005), and (iii) cigarette-smoking in these patients modulates the expression of TD and other movement disorders. These represent both neurologic-psychiatric comorbidity (Decina et al., 1990; Menza et al., 1991; Yassa et al., 1987) as well as nicotinic-dopaminergic comorbidity (Levin et al., 1996; Morens et al., 1995; Sandyk, 1993). Cigarette smoking is a behaviour that provides information about schizophrenia that may be applicable in several aspects (Hughes et al., 1986; Jann et al., 1986; Sandyk and Kay, 1991); e.g., it appears that nicotine withdrawal may exacerbate schizophrenic symptoms (Dalack and Meador-Woodruff, 1996;

but see Dalack et al., 1999). It is worth noting that typical and atypical neuroleptics affected smoking in schizophrenic patients differentially: haloperidol increased whereas clozapine decreased smoking (McEvoy et al., 1995a, b). Continued study of the role of nicotine receptors in schizophrenia is warranted.

Riederer's overview (Mojacar paper) implied that neurochemical dysfunctions in loop systems associated with motor behaviour, psychomotor behaviour (or, conversely, retardation) or psychiatric behaviour induce the risk of vulnerability in the respective unaffected pathway. From the point of view of staging (Braak et al., 2003a, b) the early diagnosis of degenertive disorders is essential. In this regard an increased echogenicity of the substantia nigra, detected with transcranial ultrasound, has been observed in PD patients and a small proportion of healthy adults (Berg et al., 1999, 2001a, b, 2002; Iova et al., 2004). Zecca et al. (2005) assayed for iron, ferritin, and neuromelanin content following postmortem scanning of normal subjects' brains to measure substantia nigra echogenicity. A significant positive correlation was found between the echogenic area of the SN and the concentration of iron, H- and L-ferritins. Multivariate analysis carried out in relation to iron content showed a significant negative correlation between echogenicity and neuromelanin content of the substantia nigra. In PD, a typical loss of neuromelanin and increase of iron is observed in this brain area. Certainly, the involvement of iron, ferritins and neuromelanin in substantia nigra and locus coeruleus neuropathology implicated in PD is accumulating (Zecca et al., 2004; and see below). For instance, the two regions share certain similarities, e.g. both are pigmented because of neuromelanine and both contain catecholaminergic neurons, and there is neuronal loss in both in PD, AD and Down's syndrome. Remarkably, Zarow et al. (2003), examining a sample comprising cases of pathologically confirmed AD ($n = 86$), PD ($n = 19$) and healthy elderly controls ($n = 13$), found that the AD cases showed neuron loss of the order: locus coeruleus > nucleus basalis > substantia nigra, and PD cases: locus coeruleus > substantia nigra > nucleus basalis. Thus, the greatest loss of neurons in both AD and PD was obtained in the locus coeruleus. From the point of view of staging, the significant correlations between neuronal loss in the locus coeruleus and nucleus basalis (but not SN) in both PD and AD imply that these two cell body-containing regions may share common pathogenetic susceptibilities relevant to the neurogenetic process.

Mehler-Wex, Riederer and Gerlach (under review) have discussed recent evidence that a dopamine-related imbalance of basal ganglia neurocircuitries contributes the essential pathophysiology underlying PD, schizophrenia and attention deficit hyperactivity disorder (ADHD). The basal ganglia include the striatum, caudate nucleus, putamen, medial and lateral segments of the globus pallidus and the amygdala, with functional connections to the subthalamic nucleus and substantia nigra (Graybiel, 1990). In disorders involving dysfunctional movement expression, clusters of striatal neurons (matrisomes) become abnormally active in inappropriate contexts leading to inhibition of GPi or SNpr neurons that would normally be active to supress unwanted movements or inactive in the initiation of motor activation. The inhibition/excitation of GPi or SNpr neurons may lead to the disinhibition/inhibition of thalamocortical circuits, the final common pathway (see fig. 11 in Mehler-Wex et al., 2006). Activity-dependent dopamine effects may phasically reinforce, inappropriately, these activity patterns leading to stereotyped behaviours (Albin, 2006; Mink, 2006). Essentially, Mehler-Wex et al. (under review) imply that the a critical consequence will be overactivity of basal ganglia output sites with concomitant inhibition of thalamo-cortical drive (see above). In schizophrenia, the hyperactive nature of inhibitory dopamine D_2 receptor-mediated transmission disinhibits the thalamus thereby resulting in cortical overstimulation; this may underlie the end-products of faulty perceptual, attentional and information processing functions and affective regulation. Related dopaminergic neuropathology may contribute to symptom expression in ADHD. In this regard, Lee et al. (2006) reported that high-frequency stimulation of the subthalamic nucleus increased action potential firing there only during the initial stimulation period and was followed by a cessation of firing over the remainder of stimulation. Electrical stimulation of the subthalamic nucleus with 15 pulses elicited stimulus time-locked increases in striatal dopamine efflux with maximal peak effects occurring at 50 Hz frequency and 300 μA intensity. Extended subthalamic nucleus stimulation (1000 pulses at 50 Hz; 300 μA) elicited a similar peak increase in striatal dopamine efflux that was followed by a relatively lower steady-state elevation in extracellular dopamine over the course of stimulation. In contrast, extended stimulation immediately adjacent and dorsal to the subthalamic nucleus resulted in an 11-fold greater increase in dopamine efflux that remained elevated over the course of the stimulation. These findings implicate the subthalamic nuclei in dopamine release that may function in an antiparkinsonian manner and/or a proschizophrenic manner. Perhaps this account also identifies stages of neurodysfunction like those identified by Braak et al. (2003a, b) that may underlie all three of the disorders mentioned above.

Archer and Fredriksson (under review) described the influence of postnatal iron overload upon the interactive role of dopaminergic and noradrenergic pathways in mice. These pathways contribute to the expressions of movement disorder and psychotic behaviours. Excessive iron deposits in the brain may generate cytotoxic free radical formation (Ben-Shachar and Youdim, 1990; Ben-Shachar et al., 1991) and alterations in iron metabolism play an important role in many neurologic diseases (Evans, 1993; Olanow, 1992; Strong et al., 1993). Postnatal iron overload at doses of 7.5 mg/kg (administered on days 10–12 post partum) and above induced a behavioural syndrome consisting of an initial hypoactivity followed by a later hyperactivity, in adult mice tested for 60 min. Following postnatal iron overload, subchronic treatment with the neuroleptic compounds, clozapine and haloperidol, dose-dependently reversed the initial hypoactivity and later hyperactivity induced by the metal. Furthermore, dopamine D_2 receptor supersensitivity (as assessed using the apomorphine-induced behaviour test) was directly and positively correlated with iron concentrations in the basal ganglia. The selective denervation of noradrenaline terminals using the selective noradrenaline neurotoxin, DSP4, followed by administration of the selective dopamine neurotoxin, MPTP, has been employed as an experimental model for 'accelerated' PD, reflecting a striatal dopamine and central noradrenaline deficiency (Fornai et al., 1997; Marien et al., 1993; Nishi et al., 1991). Brain noradrenaline denervation, using the selective noradrenaline neurotoxin, DSP4, prior to administration of the selective dopamine neurotoxin, MPTP, exacerbated both the functional (hypokinesia) and neurochemical (dopamine depletion) effects of the latter neurotoxin. Treatment with L-Dopa restored motor activity only in the animals that had not undergone noradrenaline denervation. Finally, C57/BL6 mice were administered either postnatal iron (Fe^{2+} 7.5 mg/kg, on postnatal days 10–12) or vehicle, followed by either DSP4 (50 mg/kg, s.c., 30 min after injection of zimeldine, 20 mg/kg, s.c.) or vehicle (saline) at 63 days of age. Postnatal iron administration exacerbated the bradykinesia induced by MPTP and virtually abolished all spontaneous motor activity in noradrenaline-denervated mice that were MPTP-treated. Suprathreshold doses (20 mg/kg) of L-Dopa invariably restore motor activity in MPTP mice: nevertheless, postnatal iron administration reduced markedly the restoration of motor activity by suprathreshold L-Dopa (20 mg/kg) following a 60-min habituation to the test chambers. Pretreatment with DSP4 effectively eliminated the restorative effect of L-Dopa in the MPTP mice. Postnatal iron administration caused enduring higher levels of total iron content in all the groups with an increased level in mice treated with DSP4 followed by MPTP. From a perspective based on the staging findings of Braak et al. (2003a, b), these divergent findings confirm the developmental and predispositional role of postnatal iron overload and prior denervation of noradrenaline upon dopaminergic functional expression and indicate a permanent vulnerability both in the noradrenergic and dopaminergic pathways following the postnatal infliction of an iron overload.

In conclusion, the findings of Braak and co-workers showed that diseases such as PD and AD have stages associated with progressive neuronal loss from specific brain regions. In the early stages, affected individuals may be relatively symptom-free or may show symptoms not previously associated with the disorder that they eventually develop. Thus, there is a natural comorbidity of some symptom clusters associated with different stages of an illness. This comorbidity has influenced approaches to drug development as was shown in the work of Youdim and coworkers (in press). It has been implied by the findings of interactive effects of different monoamines in models of TD (Kostrzewa et al., in press) and of complex neurotransmitter abnormalities in PD and AD (Archer and Fredriksson, under review; Mehler-Wex et al., under review). Taken together, results suggest that a continued focus on a number of neuropsychiatric diseases as progressive disorders may lead to further advances in understanding their etiology and in developing better therapeutics.

Acknowledgement

Despite the Herculean burdens, originating from complications arising from venue, travel and logistics, Tomas Palomo and the Fundacion Cerebro y Mente succeeded brilliantly in assembling an uniquely renowned group of leading clinicians and neuroscientists. Ignoring daunting odds, he succeeded beyond all reasonable expectation in bringing together, cementing and motivating this prestigious array of Invited Speakers, notwithstanding all manner of insuperable obstacles. The "Implications of Comorbidity for Etiology and Treatment of Neuropsychiatric Disorders" were unravelled under the benign influence of the warm and gentle ambience in the south-western corner of Andalucia, at the Parador de Mazagon (Huelva).

References

Aarsland D, Perry R, Larsen JP, McKeith IG, O'Brien JT, Perry EK, Burn D, Ballard CG (2005) Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry 66: 633–637

Adler LE, Hoffer LJ, Griffith J, Waldo MC, Freedman R (1992) Normalization nicotine of deficit auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry 32: 607–616

Aguilar MC, Gurpegui M, Diaz FJ, De Leon J (2005) Nicotine dependence and symptoms in schizophrenia: naturalistic study of complex interactions. Br J Psychiatry 186: 215–221

Albin RL (2006) Neurobiology of basal ganglia and Tourette's syndrome: striatal and dopamine function. Adv Neurol 99: 89–98

Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366–375

Anthony JC, Warner LA, Kessler (1994) Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol 2: 244–268

Arends YM, Duyckaerts C, Rozemuller JM, Eikelenboom P, Hauw JJ (2000) Microglia, amyloid and dementia in alzheimer disease. A correlative study. Neurobiol Aging 21: 39–47

Arnold SE, Hyman BT, Flory J, Damasio AR, van Hoesen GW (1991) The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cerebral Cortex 1: 103–116

Bancher C, Brunner C, Lassmann H, Budka H, Jellinger K, Wiche G et al (1989) Accumulation of abnormally phosphorylated tau preceedes the formation of neurofibrillary tangles in Alzheimer's disease. Brain Res 477: 90–99

Ben-Shachar D, Youdim MBH (1990) Neuroleptic-induced supersensitivity and brain iron: I. Iron deficiency and neuroleptic-induced dopamine D2 receptor supersensitivity. J Neurochem 54: 1136–1141

Ben-Shachar D, Pinhassi B, Youdim MB (1991) Prevention of neuroleptic-induced dopamine D2 receptor supersensitivity by chronic iron salt treatment. Eur J Pharmacol 202: 177–183

Berg D, Becker G, Zeiler B, Tucha O, Hofmann E, Preier M, Benz P, Jost W, Reiners K, Lange KW (1999) Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. Neurology 53: 1026–1031

Berg D, Jabs B, Merschdorf U, Beckmann H, Becker G (2001a) Echogenicity of substantia nigra determined by transcranial ultrasound correlates with severity of parkinsonian symptoms induced by neuroleptic therapy. Biol Psychiatry 50: 463–467

Berg D, Siefker C, Ruprecht-Dorfler P, Becker G (2001b) Relationship of substantia nigra echogenicity and motor function in elderly subjects. Neurology 56: 13–17

Berg D, Roggendorf W, Schroder U, Klein R, Tatschner T, Benz P, Tucha O, Preier M, Lange KW, Reiners K, Gerlach M, Becker G (2002) Echogenicity of the substantia nigra: association with increased iron content and marker for susceptibility to nigrostriatal injury. Arch Neurol 59: 999–1005

Borsini F, Meli A (1988) Is the forced swimming test a suitable model for revealing antidepressant activity. Psychopharmacology 94: 147–160

Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82: 239–259

Braak H, Braak E (1994) Pathology of Alzheimer's disease. In: Calne DB (ed) Neurodegenerative diseases. Saunders, Philadelphia, pp 585–613

Braak H, Braak E, Mandelkow EM (1994) A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neurophil threads. Acta Neuropathol 87: 554–567

Braak H, Braak E, Yilmazer K, Bohl J (1996) Functional anatomy of human hippocampal formation and related structures. J Child Neurol 11: 265–275

Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 18: 351–357

Braak H, Braak E (1999) Temporal sequence of Alzheimer's disease-related pathology. In: Peters A, Morrison P (eds) Neurodegenerative and Age-related Changes in Structure and Function of the Cerebral Cortex. Vol. 14. Kluwer Academic/Plenum Publications, New York, pp 475–512

Braak H, Del Tredici K, Braak E (2000) Spectrum of pathology. In: Peterson R (ed) Mild 1Cognitive Impairment. Oxford University Press, New York, pp 149–189

Braak H, Del Tredici K (2004) Alzheimer's disease: intraneuronal alterations precede insoluble amyloid-β formation. Neurobiol Aging 25: 713–718

Braak H, Del Tredici KD, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E (2003a) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24: 197–211

Braak H, Rüb U, Gai M, Del Tredici KD (2003b) Idiopathic Parkinson' disease: possible routes by which vulnerable neuron types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 110: 517–536

Braak H, Del Tredici K, Braak E (2003c) Spectrum of pathology. In: Peterson R (ed) Mild Cognitive Impairment. Oxford University Press, New York, pp 149–189

Brus R, Kostrzewa RM, Perry KW, Fuller RW (1994) Supersensitization of the oral response to SKF 38393 in neonatal 6-hydroxydopamine-lesioned rats is eliminated by neonatal 5,7-dihydroxytryptamine treatment. J Pharmacol Exp Ther 268: 231–237

Casey DE (1989) Clozapine: neuroleptic-induced EPS and tardive dyskinesia. Psychopharmacology 99: 47–53

Casey DE (1991) Neuroleptic drug-induced extrapyramidal syndromes. Schizophr Res 4: 109–120

Casey DE (1994) Motor and mental aspects of acute extrapyramidal syndromes. Acta Psychiatr Scand 380: 14–20

Dalack GW, Meador-Woodruff JH (1996) Smoking, smoking withdrawal and schizophrenia: case reports and a review of the literature. Schizophr Res 22: 133–141

Dalack GW, Becks L, Meador-Woodruff JH (1998a) Tardive dyskinesia, clozapine, and treatment response. Prog Neuro-Psychopharmacol Biol Psychiatry 22: 567–573

Dalack GW, Healy DJ, Meador-Woodruff JH (1998b) Nicotine dependence in schizophrenia: clinical and laboratory findings. Am J Psychiatry 155: 1490–1501

Dalack GW, Becks L, Hill E, Pomerleau OF, Meador-Woodruff JH (1999) Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. Neuropsychopharmacology 21: 195–202

Daly SA, Waddington JL (1993) Behavioural evidence for ''D-1-like'' dopamine receptor subtypes in rat brain using the new isochroman agonist A 68930 and isoquinoline antagonist BW 737C. Psychopharmacology 113: 45–50

Davé M (1994) Clozapine-related tardive dyskinesia. Biol Psych 35: 886–887

Decina P, Caracci G, Sandik R, Berman W, Mukherjee S, Scapicchio P (1990) Cigarette smoking and neuroleptic-induced parkinsonism. Biol Psychiatry 28: 502–508

DeKosky S, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ (2002) Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol 51: 145–155

De Leon J, Moral L, Camunas C (1991) Clozapine and jaw dyskinesia: a case report. J Clin Psychiatry 52: 494–495

DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13: 281–285

Deniker P (1983) Discovery of the clinical use of neuroleptics. In: Parnam MJ, Bruinvels J (eds) Discoveries in Pharmacology Vol. 1: Psycho- and Neuro-pharmacology. Elsevier, Amsterdam, pp 164–180

Egan MF, Hurd Y, Ferguson J, Bachus SE, Hamid EH, Hyde TM (1996) Pharmacological and neurochemical differences between acute and tardive vacuos chewing movements induced by haloperidol. Psychopharmacology 127: 337–345

Evans PH (1993) Free radicals in brain metabolism and pathology. Br Med Bull 49: 577–587

Farde L, Wiesel FA, Haldin C, Sedvall G (1988) Central D2 dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatr 45: 71–76

Finberg JP, Lamensdorf I, Commissiong JW, Youdim MBH (1996a) Pharmacology and neuroprotective properties of rasagiline. J Neural Transm [Suppl 48]: 95–101

Finberg JP, Takeshima T, Johnston JM, Commissiong JW (1996b) Increased survival of dopaminergic neurons by rasagiline, a monoamine oxidase B inhibitor. Neuroreport 9: 703–707

Fornai F, Alessandri MG, Torracca MT, Bassi L, Corsini GU (1997) Effects of noradrenergic lesions on MPTP/MPP+ kinetics and MPTP-induced nigrostriatal dopamine depletions. J Pharmacol Exp Ther 283: 100–107

Francis PT, Palmer AM, Snape M, Wilcock GK (1999) The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 66: 137–147

Francis PT, Nordberg A, Arnold SE (2005) A preclinical view of cholinesterase inhibitors in neuroprotection: do they provide more than symptomatic benefits in Alzheimer's disease? TIPS 28: 104–111

Gal S, Zheng H, Fridkin M, Youdim MBH (2005) Novel multifunctional neuroprotective chelator-monoamine oxidase inhibitor drugs for neurodegenerative diseases. In vivo selective brain monoamine oxidase inhibition and prevention of MPTP-induced striatal dopamine depletion. J Neurochem 95: 79–88

Giacobibi E (2004) Cholinesterase inhibitors: new roles and therapeutic alternatives. Pharmacol Res 50: 433–440

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

Gong L, Kostrzewa RM, Fuller RW, Perry KW (1992) Supersensitization of 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

Gong L, Kostrzewa RM, Brus R, Fuller RW, Perry KW (1993a) Ontogenetic SKF 38393 treatments sensitize dopamine D_1 receptors in neonatal 6-OHDA-lesioned rats. Dev Brain Res 76: 233–238

Gong L, Kostrzewa RM, Fuller RW, Perry KW (1993b) Dose-related effects of a neonatal 6-OHDA lesion on SKF-38393-and m-chlorophenylpiperazine-induced oral activity responses of rats. Dev Brain Res 76: 233–238

Gong L, Kostrzewa RM, Li C (1994) Neonatal 6-hydroxydopamine and SKF 38393 treatments alter dopamine D_1 receptor mRNA levels: absence of other neurochemical associations with the enhanced behavioural responses of lesioned rats. J Neurochem 63: 1282–1290

Gouras GK, Almeida CG, Takahashi RH (2005) Intraneuronal Abeta accumulation and origin of plaques in Alzheimer's disease. Neurobiol Aging 26: 1235–1244

Graybiel AM (1990) Neurotransmitters and neuromodulators in the basal ganglia. Trend Neurosci 13: 244–264

Huang N-Y, Kostrzewa RM (1994) Persistent oral dyskinesias in haloperidol-withdrawn neonatal 6-hydroxydopamine-lesioned rats. Eur J Pharmacol 253: 163–166

Huang W, Chen Y, Shohami E, Weinstock M (1999) Neuroprotective effect of rasagiline, a selective monoamine oxidase-B inhibitor, against closed head injury in the mouse. Eur J Pharmacol 366: 127–135

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA (1986) Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 413: 993–997

Hyman BT, van Hoesen GW, Damasio AR, Barnes CL (1984) Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 225: 1168–1170

Iova A, Garmashov A, Androuchtchenko N, Kehrer M, Berg D, Becker G, Garmashov Y (2004) Postnatal decrease in substantia nigra echogenicity. Implications for the pathogenesis of Parkinson's disease. J Neurol 251: 1451–1454

Jann MW, Saklad SR, Ereshefsky L, Richards AL, Harrington CA, Davis CM (1986) Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. Psychopharmacology 90: 468–470

Jeste DV, Caliguiri MP (1993) Tardive dyskinesia. Schizophr Bull 19: 303–315

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

Kalian M, Lerner V, Goldman M (1993) Atypical variants of tardive dyskinesia, treated by a combination of clozapine and propranolol and clozapine with tetrabenazine. J Ment Dis 181: 649–651

Kane J, Woener M, Pollack S, Safferman A, Lieberman JA (1993) Does clozapine cause tardive dyskinesia? J Clin Psychiatry 54: 327–330

Klyubin I, Walsh DM, Lemere CA, Cullen WK, Shankar GM, Betts V, Spooner ET, Jiang L, Anwyl R, Selkoe DJ, Rowan MJ (2005) Amyloid beta protein immunotherapy neutralizes Abeta oligomers that disrupt synaptic plasticity in vivo. Nat Med 11: 556–561

Koshikawa N, Aoki S, Tomiyama M, Maruyama Y, Kobayashi M (1987) Sulpiride injection into the dorsal striatum increases meth amphetamine-induced gnawing in rats. Wur J Pharmacol 133: 119–125

Kostrzewa RM (1995) Dopamine receptor supersensitivity. Neurosci Biobehav Rev 19: 1–17

Kostrzewa RM, Gong L (1991) Supersensitized D1 receptors mediate enhanced oral activity after neonatal 6-OHDA. Pharmacol Biochem Behav 39: 677–682

Kostrzewa RM, Hamdi A (1991) Potentiation of spiperone-induced oral activity after neonatal 6-hydroxydopamine. Pharmacol Biochem Behav 38: 215–218

Kostrzewa RM, Brus R, Perry KW, Fuller RW (1993) Age-dependence of 6-hydroxydopamine lesion on SKF 38393- and m-chlororphenylpiperazine-induced oral activity responses in rats. Dev Brain Res 76: 889–898

Kostrzewa RM, Nowak P, Kostrzewa JP, Brus R (2006) Modeling tardive dyskinesia: predictive new treatment. Neurotoxicity Res (in press)

Krystal JH, D'souza DC, Gallinat J, Driesen N, Abi-Dargham A, Petrakis I, Heinz A, Pearlson G (2006) The vulnerability to alcohol and substance abuse in individuals diagnosed with schizophrenia. Neurotoxicity Res (in press)

Kurz M, Hummer M, Oberbauer H, Fleischacker WW (1995) Extrapyramidal side effects of clozapine and haloperidol. Psychopharmacology 118: 52–56

Lamberti JS, Bellnier T (1993) Clozapine and tardive dystonia. J Ment Dis 181: 137–330

Lee KH, Blaha CD, Harris BT, Cooper S, Hitti FL, Leiter JC, Roberts DW, Kim U (2006) Dopamine efflux in the rat striatum evoked by electrical stimulation of the subthalamic nucleus: potential mechanism of action in Parkinson's disease. Eur J Neurosci 23: 1005–1014

Leentjens AF (2004) Depression in Parkinson's disease: conceptual issues and clinical challenges. J Geriatr Psychiatry Neurol 17: 120–126

Levin ED, See RE, South D (1989) Effects of dopamine D1 and D2 receptor antagonists on oral activity in rats. Pharmacol Biochem Behav 34: 43–48

Levin ED, Wilson W, Rose JE, McEvoy J (1996) Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 15: 429–436

Levkovitch Y, Kronenberg J, Kayser N, Zvyagelski M, Gaoni B, Gadoth N (1995) Clozapine for tardive dyskinesia in adolescents. Brain Dev 17: 213–215

Lewander T (1994) Neuroleptics and neuroleptic-induced deficit syndrome. Acta Psychiatr Scand [Suppl 380]: 8–13

Lieberman JA, Saltz BL, Johns CA, Pollack S, Borenstein M, Kane J (1991) The effects of clozapine on tardive dyskinesia. Br J Psychiatr 158: 503–510

Littrell K, Magill AM (1993) The effect of clozapine on preexisting tardive dyskinesia. J Psychosoc Nurs 31: 14–18

Marien MR, Briley M, Colpaert FC (1993) Noradrenaline depletion exacerbates MPTP-induced striatal dopamine loss in mice. Eur J Pharmacol 236: 487–489

Maruyama W, Weinstock M, Youdim MBH, Nagai M, Naoi M (2003) Anti-apoptotic action of anti-Alzheimer drug, TV3326 [(N-propargyl)-(3R)-

aminoindan-5-yl]-ethyl methyl carbamate, a novel cholinesterase-monoamine oxidese inhibitor. Neurosci Lett 341: 233–236

Maruyama W, Nitta A, Shamoto-Nagai M, Hirata Y, Akao Y, Youdim MBH, Furukawa S, Nabeshima T, Naoi M (2004) N-Propargyl-1 (R)-aminoindan, rasagiline, increases glial cell line-derived neurotrophic factor (GDNF) in neuroblastoma SH-SY5Y cells through activation of NF-kappaB transcription factor. Neurochem Int 44: 393–400

McDonald WM, Richard IH, DeLong MR (2003) Prevalence, etiology, and treatment of depression in Parkinson's disease. Biol Psychiatry 54: 363–375

McEvoy JP, Freudenreich O, Levin ED, Rose JE (1995a) Haloperidol increases smoking in patients with schizophrenia. Psychopharmacology 119: 124–126

McEvoy JP, Freudenreich O, McGee M, VanderZwaag C, Levin ED, Rose J (1995b) Clozapine decreases smoking in patients with schizophrenia. Biol Psychiatry 37: 550–552

Mehler-Wex C, Duvigneau JC, Hart RT, Ben-Shachar D, Warnke A, Gerlach M (2006) Increased mRNA levels of the mitochondrial complex 175-KDa subunit: A potential peripheral marker of early onset schizophrenia? Eur child Adolesc Psychiatry, in press

Menza MA, Grossman N, Van Horn M, Cody R, Forman N (1991) Smoking and movement disorders in psychiatric patients. Biol Psychiatry 30: 109–115

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50: 381–425

Mink JW (2006) Neurobiology of basal ganglia and Tourette's syndrome: basal ganglia circuits and thalamocortical outputs. Adv Neurol 99: 99–106

Morens DM, Grandinetti A, Reed D, White LR, Ross GW (1995) Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? Neurology 45: 1041–1045

Naber D, Leppig M, Grohmann R, Hippius H (1989) Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia – A retrospective study of 387 patients. Psychopharmacology 99: S73–S76

Nair C, Abraham G, De Leon J, Stanilla JK, Josiassen RC, Simpson G (1996) Dose-related effects of clozapine on tardive dyskinesia among "Treatment-refractory" patients with schizophrenia. Biol Psychiatry 39: 529–530

Nishi K, Kondo T, Narabayashi H (1991) Destruction of norepinephrine terminals in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice reduces locomotor activity induced by L-dopa. Neurosci Lett 123: 244–247

O'Brien CP, Charney DS, Lewis L, Cornish JW, Post RM, Woody GE, Zubieta JK, Anthony JC, Blaine JD et al (2004) Priority actions to improve the care of persons with co-occuring substance abuse and other mental disorders: a call to action. Biol Psychiatry 56: 703–713

Olanow CW (1992) Magnetic-resonance-imaging in parkinsonism. Neurology in the Clinic 10: 405–420

Pakaski M, Kasa P (2003) Role of acetylcholinesterase inhibitors in the metabolism of amyloid precursor protein. Curr Drug Targets CNS Neurol Disord 2: 163–171

Palomo T, Beninger RJ, Kostrzewa RM, Archer T (2004) Gene-environment interplay in affect and dementia: emotional modulation of cognitive expression in personal outcomes. Neurotoxicity Res 6: 159–173

Przuntek H, Müller T, Reiderer P (2004) Diagnostic staging of Parkinson's disease. J Neural Transm 111: 201–216

Racchi M, Sironi M, Caprera A, Konig G, Govoni S (2001) Acetylcholinesterase inhibitors: novel activities of old molecules. Pharmacol Res 50: 441–451

Racchi M, Mazzucchelli M, Porello E, Lanni C, Govoni S (2004) Acetylcholinesterase inhibitors: novel activities of old molecules. Pharmacol Res 50: 441–451

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264: 2511–2518

Rupniak NMJ, Jenner P, Marsden CD (1985) Pharmacological characterisation of spontaneous or drug-associated purposeless chewing movements in rats. Psychopharmacology 85: 71–79

Sacco KA, Bannon KL, George TP (2004) Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. J Psychopharmacol 18: 457–474

Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, Jatlow PI, Wexler BE, George TP (2005) Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. Arch Gen Psychiatry 62: 649–659

Sandyk R (1993) Cigarette smoking: effects on cognitive functions and drug-induced parkinsonism in chronic schizophrenia. Int J Neurosci 70: 193–197

Sandyk R, Kay SR (1991) Tobacco addiction as a marker of age at onset of schizophrenia. Intern Neurosci 57: 259–262

Sarter M, Nelson CL, Bruno JP (2005) Cortical cholinergic transmission and cortical information processing in schizophrenia. Schizophrenia Bull 31: 117–138

Schmidt W, Beninger RJ (2006) Behavioural sensitization in addiction, schizophrenia, Parkinson's disease and dyskinesia. Neurotoxicity Res (in press)

Shih RA, Belmonte Pl, Zandi PP (2004) A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. Int Rev Psychiatry 16: 260–283

Sterling J, Herzig Y, Goren T, Finkelstein N, Lerner D, Goldenberg W, Miskolczi L, Molnar S, Rantal F et al (2002) Novel dual inhibitors of AchE and MAO derived from hydroxy aminoindan and phenylethylamine as potential treatment for Alzheimer's disease. J Med Chem 45: 5260–5279

Strong R, Mattamal M, Andorn A (1993) Free radicals in aging. In: Free radicals, the aging brain, and age-related neurodegenerative disorders. CRC Press, Boca Raton, FL, pp 223–246

Tamminga CA, Thaker GK, Moran M, Kakigi T, Gao XM (1994) Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 55 [Suppl]: 102–106

Thal DR, Rub U, Schulz C, Sassin I, Ghebremedhin E, Del Tredici K et al (2000) Sequence of Aβ protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol 59: 733–748

Thal DR, Del Tredici K, Braak H (2004) Neurodegeneration in normal brain aging and disease. Sci Aging Knowledge Environ 9: 26–34

Van Hoesen GW, Hyman BT (1990) Hippocampal formation: anatomy and the patterns of pathology in Alzheimer's disease. Prog Brain Res 83: 445–457

Veazey C, Aki SO, Cook KF, Lai EC, Kunik ME (2005) Prevalence and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 17: 310–323

Waddington JL, Cross AJ, Gamble SJ, Bourne RC (1983) Spontaneous orofacial dyskinesia and dopaminergic function in rats after 6 months of neuroleptic treatment. Science 220: 530–532

Waddington JL, Murray AM, O'Callaghan E, Larkin C (1989) Orofacial dyskinesia: D-1/D-2 dopamine receptors in rodents, and familial/obstetric correlates of tardive dyskinesia in schizophrenia. In: Crossman AR, Sambrook MA (eds) Neural mechanisms in disorders of movement. Libbey, London, pp 359–366

Weinreb O, Bar-Am O, Amit T, Chillag-Talmor O, Youdim MBH (2004) Neuroprotection via pro-survival protein kinase C isoforms associated with Bcl-2 family members. FASEB J 18: 1471–1473

Weinstock M, Goren T, Youdim MBH (2000a) Development of a novel neuroprotective drug (TV3326) for the treatment of Alzheimer's disease, with cholinesterase and monoamine oxidase inhibitory activities. Drug Dev Res 50: 216–222

Weinstock M, Bejar C, Wang RH, Poltyrev T, Gross A, Finberg JP, Youdim MBH (2000b) TV3326, a novel neuroprotective drug with cholinesterase and monoamine oxides inhibitory activities for the treatment of Alzheimer's disease. J Neural Transm 60: 157–169

Weinstock M, Kirschbaum-Slager N, Lazarovici P, Bejar C, Youdim MBH (2001) Neuroprotective effects of novel cholinesterase inhibitors derived from rasagiline as potential anti-Alzheimer drugs. Ann NY Acad Sci 939: 148–162

Wirshing WC, Phelan CK, Van Putten T, Marder SR (1990) Effects of clozapine on treatment-resistent akathisia and concomitant tardive dyskinesia. J Clin Psychopharmacol 10: 371–373

Wu Rm, Chen RC, Chiueh CC (2000) Effect of MAO-B inhibitors on MPP+ toxicity in vivo. Ann NY Acad Sci 899: 255–261

Yassa R, Lal S, Korpassy A, Ally J (1987) Nicotine exposure and tardive dyskinesia. Biol Psychiatry 22: 67–72

Yi H, Maruyama W, Akao Y, Chen K, Iwasa K, Shih J, Youdim MBH, Naoi M (2005) The N-propargyline moiety of rasagiline has neuroprotective activity via mitochrondrial membrane stabilization and induction of Bcl-2. J Neural Transm 20: 1435–1463

Yogev-Falach M, Bar-Am O, Sagi Y, Weinstock M, Youdim MBH (2002) The involvement of mitogen-activated protein (MAP) kinase in the regulation of amyloid precursor protein processing by novel cholinesterase inhibitors derived from rasagiline. FASEB J 16: 1674–1676

Yogev-Falach M, Bar-Am O, Youdim MBH (2003) The importance of N-propargyline moiety in the anti-Parkinson drug rasagiline and its derivatives for MAPK-dependent amyloid precursor protein processing. FASEB J 17: 2325–2327

Youdim MBH, Gross A, Finberg JP (2001a) Rasagiline [N-propargyl-1R(+)-aminoindan, a selective and potent inhibitor of mitochondrial monoamine oxidase B. Br J Pharmacol 132: 500–506

Youdim MBH, Grunblatt E, Levites Y, Mandel (2001b) Drugs to prevent cell death in Parkinson's disease. In: Calne DB, Calne S (eds) Neuroprotection against oxidative stress and inflammatory gene expression, Vol. 86. Lippincott, Williams & Wilkins, Philadelphia, pp 115–125

Youdim MBH, Weinstock M (2002a) Novel neuroprotective anti-Alzheimer drugs with antidepressant activity derived from the anti-Parkinson drug, rasagiline. Mech Aging Dev 123: 1081–1086

Youdim MBH, Weinstock M (2002b) Molecular basis of neuroprotective activities of rasagiline and the anti-Alzheimer drug, TV3326, [(N-propargyl-(3R)-Aminoindan-5-yl)-ethyl methyl carbamate]. Cell Mol Neurobiol 21: 555–573

Youdim MBH (2003) Rasagiline: an anti-Parkinson drug with neuroprotective activity. Exp Rev Neurother 3: 737–749

Youdim MBH, Amit T, Bar-Am O, Weinreb O, Yogev-Falach M (2006) Implications of co-morbidity for etiology and treatment of neurodegenerative diseases with multifunctional neuroprotective-neurorescue drugs: Ladostigil. Neurotoxicty Res (in press)

Youssef HA, Waddington JL (1987) Morbidity and mortality in tardive dyskinesia: associations in chronic schizophrenia. Acta Psychiatr Scand 75: 74–77

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

Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingsson T, Lewis G (2003) Investigating the association between cigarette smoking and schizophrenia in a cohort study. Am J Psychiatry 160: 2216–2221

Zarow C, Lyness SA, Mortimer JA, Chui HC (2004) Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol 60: 337–341

Zecca L, Stroppolo A, Gatti A, Tampellini D, Toscani M, Gallorini M, Giaveri G, Arosio P, Santambrogio P, Fariello RG, Karatekin E, Kleinman MH, Turro N, Hornykiewicz O, Zucca FA (2004a) The role of iron and copper molecules in the neuronal vulnerability of locus coeruleus and substantia nigra during aging. Proc Natl Acad Sci USA 101: 9843–9848

Zecca L, Stroppolo A, Gatti A, Tampellini D, Toscani M, Gallorini M, Giaveri G, Arosio P, Santambrogio P, Fariello RG, Karatekin E, Kleinman MH, Turro N, Hornykiewicz O, Zucca FA (2004b) Postnatal decrease in substantia nigra echogenicity. Implications for the pathogenesis of Parkinson's disease. J Neurol 251: 1451–1454

Zecca L, Berg D, Arzberger T, Ruprecht P, Rausch WD, Musicco M, Tampellini D, Riederer P, Gerlach M, Becker G (2005) In vivo detection of iron and neuromelanin by transcranial sonography: a new approach for early detection of substantia nigra damage. Mov Disord 20: 1278–1285

Zheng H, Gal S, Weiner LM, Bar-Am O, Warshawsky A, Fridkin M, Youdim MBH (2005) Novel multifunctional neuroprotective iron chelator-monoamine oxidase inhibitor drugs for neurodegenerative diseases: in vitro studies on antioxidant activity, prevention of lipid peroxide formation and monoamine oxide inhibtition. J Neurochem 95: 68–78

Zimmerman M, Gardoni F, Marcello E, Colciaghi F, Borroni B, Padovani A, Cattabeni F, Di Luca M (2004) Acetylcholinesterase inhibitors increase ADAM10 activity by promoting its trafficking in neuroblastoma cell lines. J Neurochem 90: 1489–1499