The neurotoxic actions of quinolinic acid in the central nervous system[1]

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Received July 23, 1985

EL-DEFRAWY, S. R., R. J. BOEGMAN, K. JHAMANDAS, and R. J. BENINGER. 1986. The neurotoxic actions of quinolinic acid in the central nervous system. Can. J. Physiol. Pharmacol. **64**: 369–375.

Excitotoxins such as kainic acid, ibotenic acid, and quinolinic acid are a group of molecules structurally related to glutamate or aspartate. They are capable of exciting neurons and producing axon sparing neuronal degeneration. Quinolinic acid (QUIN), an endogenous metabolite of the amino acid, tryptophan, has been detected in brain and its concentration increases with age. The content of QUIN in the brain and the activity of the enzymes involved in its synthesis and metabolism show a regional distribution. The neuroexcitatory action of QUIN is antagonized by magnesium (Mg^{2+}) and the aminophosphonates, proposed *N*-methyl-D-aspartate (NMDA) receptor antagonists, suggesting that QUIN acts at the Mg^{2+}-sensitive NMDA receptor. Like its excitatory effects, QUIN's neurotoxic actions in the striatum are antagonized by the aminophosphonates. This suggests that QUIN neurotoxicity involves the NMDA receptor and (or) another receptor sensitive to the aminophosphonates. The neuroexcitatory and neurotoxic effects of QUIN are antagonized by kynurenic acid (KYN), another metabolite of tryptophan. QUIN toxicity is dependent on excitatory amino acid afferents and shows a regional variation in the brain. Local injection of QUIN into the nucleus basalis magnocellularis (NBM) results in a dose-dependent reduction in cortical cholinergic markers including the evoked release of acetylcholine. A significant reduction in cortical cholinergic function is maintained over a 3-month period. Coinjection of an equimolar ratio of QUIN and KYN into the NBM results in complete protection against QUIN-induced neurodegeneration and decreases in cortical cholinergic markers. In contrast, focal injections of QUIN into the frontoparietal cortex do not alter cortical cholinergic function. Animals showing central cholinergic hypofunction induced by QUIN could serve as experimental models for testing pharmacological agents aimed at improving the function of damaged cholinergic neurons.

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Les excitotoxines, telles que l'acide kaïnique, l'acide iboténique et l'acide quinolique forment un groupe de molécules qui, par leur structure, sont associées au glutamate ou à l'aspartate. Elles peuvent exciter les neurones et provoquer une dégénérescence neuronale qui épargne sur les axones. On a détecté de l'acide quinolinique (QUIN), un métabolite endogène de l'aminoacide tryptophane, dans le cerveau et on a observé que sa concentration augmentait avec l'âge. La concentration de QUIN dans le cerveau ainsi que l'activité de l'enzyme impliquée dans sa synthèse et son métabolisme se distribuent de façon régionale. L'action neuroexcitatrice de QUIN est antagonisée par le magnésium (Mg^{2+}) et les aminophosphonates, agonistes proposés du récepteur *N*-méthyl-D-aspartate (NMDA), suggérant que le QUIN agit au site du récepteur NMDA sensible au Mg^{2+}. Tout comme avec les effets excitateurs, les aminophosphonates antagonisent aussi les actions neurotoxiques de QUIN dans le striatum. Ceci suggère que la neurotoxicité de QUIN implique le récepteur NMDA et (ou) une autre récepteur sensible aux aminophosphonates. Les effets neuroexcitateurs et neurotoxiques de QUIN sont antagonisés par l'acide kynurénique (KYN), un autre métabolite du tryptophane. La toxicité de QUIN est fonction des afférences des aminoacides excitateurs et montre une variation régionale dans le cerveau. L'injection locale de QUIN dans le nucleus basalis magnocellularis (NBM) résulte en une réduction dose-dépendants des marqueurs cholinergiques corticaux, incluant la libération évoquée d'acétylcholine. Une réduction significative de la fonction cholinergique corticale est maintenue pendant une période de 3 mois. La co-injection d'une concentration équimolaire de QUIN et de KYN dans le NBM résulte en une protection complète contre la neurodégénérescence induite par QUIN et contre les diminutions des marqueurs cholinergiques corticaux. À l'opposé, des injections focales de QUIN dans le cortex fronto-pariétal n'altèrent pas la fonction cholinergique corticale. Les animaux montrant une hypofonction cholinergique centrale induite par QUIN peuvent servir de modèles expérimentaux pour tester les agents pharmacologiques destinés à améliorer la fonction des neurones cholinergiques altérés.

[Traduit par le journal]

Introduction

The discovery of excitotoxins, a group of molecules which are structurally related to glutamic or aspartic acid, has made an important contribution to the field of neurobiology. These substances, under appropriate conditions, are also capable of producing neuronal degeneration while sparing axons of passage (Olney et al. 1974; McGeer et al. 1978; Olney 1978; Kohler et al. 1979; Schwarcz et al. 1979). Kainic acid (KA) and ibotenic acid (IBO) are two examples of excitotoxins that are among the most commonly used compounds in this group of chemicals (reviewed by Schwarcz et al. 1984).

Initial studies involving focal injection of KA or IBO into the striatum or hippocampus of experimental animals resulted in a morphological and biochemical profile resembling that observed in the brains of patients with Huntington's disease or epilepsy (McGeer and McGeer 1976; Coyle and Schwarcz 1976; Coyle et al. 1978; Fibiger 1978; Nadler 1979; Ben-Ari et al. 1981). Similarities between experimental excitotoxic lesions and human neuropathology led to the proposal that the body

[1]This paper was presented at a symposium of the Canadian Federation of Biological Societies entitled "Cholinergic Mechanisms. I. Function and Dysfunction of Cholinergic Neurones. II. Neurotoxicity Associated with Altered Cholinergic Function." This symposium was held at the University of Toronto, Toronto, Ont., Canada, June 18, 1985.

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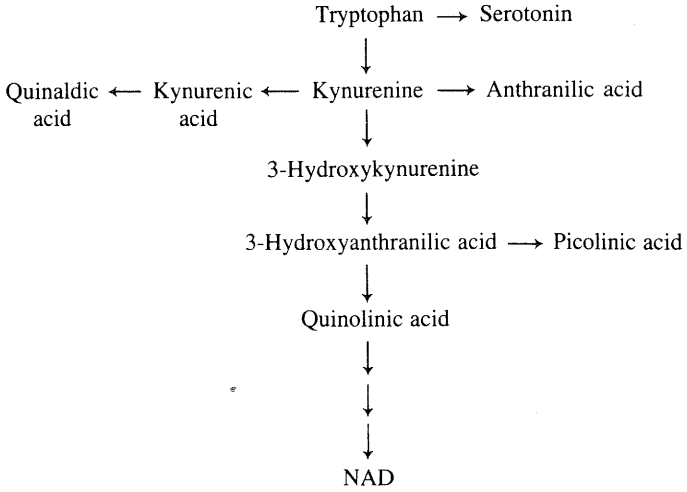

FIG. 1. Metabolic pathway of tryptophan showing some of the major metabolites. Adapted from Brown, 1980.

produces endogenous excitotoxins that might play a role in certain neurodegenerative disease states (Schwarcz et al. 1984). One of the more promising candidates for such a role is quinolinic acid.

General review

Metabolism and distribution of quinolinic acid

The role of quinolinic acid (QUIN) in the central nervous system has recently been reviewed by Stone and Connick (1985). Quinolinic acid (pyridine-2,3-dicarboxylic acid), an intermediate in the kynurenine pathway, is a metabolite of the essential amino acid, tryptophan (Fig. 1) (Brown 1980). In contrast with the peripheral metabolic pathway, the cerebral kynurenine pathway is a minor one (Gal and Sherman 1980). The enzyme responsible for the synthesis of QUIN, 3-hydroxyanthranilic acid oxygenase (3-HAO), has recently been measured in rat brain, and a regional variation in activity was observed (Foster and Schwarcz 1984). The order of activity is olfactory bulb > frontal cortex, hippocampus, striatum, hypothalamus > cerebellum and spinal cord (Foster and Schwarcz 1984). The enzyme catalyzing the breakdown of QUIN to nicotinic acid mononucleotide (which is further converted to NAD) has also been detected in rat (Foster, Miller et al. 1985; Foster, Zinkand et al. 1985) and human brain (Foster, Miller et al. 1985). This enzyme, quinolinic acid phosphoribosyltransferase (QPRT), is magnesium (Mg^{2+})-dependent and also shows a regional distribution in brain (Table 1). The brain area with the highest QPRT activity is the olfactory bulb and regions with the lowest activity include the frontal cortex, striatum, hippocampus, and the retina (Foster, Zinkand et al. 1985).

QUIN has been detected in the brains of several mammalian species including man (Wolfensberger et al. 1983; Moroni, Lombardi, Carla et al. 1984; Moroni, Lombardi, Moneti et al. 1984). In the rat CNS, QUIN is unevenly distributed (Table 1), the highest concentration being in the cortex and hippocampus. Perkins and Stone reported a regional distribution in the sensitivity of central neurons to QUIN; the cortex shows a high degree of sensitivity while other areas of the brain are less sensitive to its action (Perkins and Stone 1983*a*, 1983*b*). Thus, as suggested by Moroni, Lombardi, Carla et al. (1984), the area containing the highest concentration of QUIN, the cerebral cortex, is also the richest in specific receptors activated by this agent (Moroni, Lombardi, Carla et al. 1984). Since extracellular QUIN does not appear to be taken up or metabolized by neurons (Foster, Miller et al. 1984), application of QUIN to neurons would result in prolonged synaptic activity.

Administration of tryptophan to rats not only increases the concentration of brain 5-hydroxytryptamine (5-HT), but also that of QUIN (Moroni, Lombardi, Carla et al. 1984), while a reduction in brain tryptophan decreases levels of both substances. Although 5-HT and QUIN share a common precursor, they appear to be located in separate compartments since the regional distribution of 5-HT does not parallel that of QUIN. In addition, 5,7-dihydroxytryptamine, which depletes stores of 5-HT, does not influence the concentration of QUIN (Moroni, Lombardi, Carla et al. 1984).

In rats, the concentration of cortical QUIN increases with age; from 1.6 ± 0.3 nmol/g wet weight at 3 months of age to 4.5 ± 0.9 nmol/g wet weight at 30 months of age (Moroni, Lombardi, Moneti et al. 1984). Morphological signs of toxicity have been observed in cultures of striatal cells following exposure to as little as 10 μM QUIN (Whetsell and Schwarcz 1983); this concentration approaches that found in some older animals (Moroni, Lombardi, Moneti et al. 1984).

Neuroexcitation

Perkins and Stone were the first to show that QUIN was a neuroexcitant (Stone and Perkins 1981; Perkins and Stone 1982, 1983*a*, 1983*b*). The neuroexcitatory action of QUIN is thought to be mediated through its action on the *N*-methyl-D-aspartate (NMDA) type of excitatory amino acid receptor. This is supported by several different observations. The NMDA receptor selective antagonist, 2-amino-5-phosphonovalerate (APV), reduces excitation produced by QUIN or NMDA to the same extent in a variety of brain regions (McLennan 1984). The *in vitro* release of striatal [^{3}H]acetylcholine ([^{3}H]ACh) induced by QUIN, and the excitation produced by its iontophoretic application, are effectively antagonized by APV and 2-amino-7-phosphonoheptanoic acid (APH), two potent NMDA receptor antagonists (Lehmann et al. 1983; Perkins and Stone 1983*a*). QUIN selectively inhibits the specific binding of [^{3}H]APH, but not that of glutamate or KA, to rat forebrain membranes (Lehmann et al. 1985). Glutamate diethylester, a quisqualate receptor antagonist (McLennan and Lodge 1979); McLennan and Liu 1982), does not block the QUIN-evoked release of [^{3}H]ACh from striatal slices (Lehmann et al. 1983). This release, however, is inhibited by Mg^{2+} suggesting that QUIN interacts with the Mg^{2+}-sensitive NMDA receptor (Lehmann et al. 1983). However, while NMDA is equipotent on cortical and spinal neurons, QUIN is approximately threefold less potent on spinal neurons than on cortical neurons (McLennan 1984). The difference between the potencies of QUIN and NMDA at these two anatomical sites is thought to reflect their interaction with two different receptors that are equally sensitive to the aminophosphonates, but that have different regional densities (Perkins and Stone 1983*b*; McLennan 1984).

Neurotoxicity

Schwarcz and co-workers (Schwarcz, Whetsell, and Mangano 1983) were the first to demonstrate that QUIN causes selective neuronal lesions. They found that focal injections of QUIN into the striatum resulted in neurochemical, behavioural, and pathological changes similar to those observed following injection of KA or IBO. Since the excitatory actions of QUIN appear to be mediated through the NMDA-type excitatory amino acid receptor, its neurotoxic actions might be expected to be

TABLE 1. Concentration of quinolinic acid (QUIN) and quinolinic acid phosphoribosyltransferase (QPRT) activity in various brain regions of the rat

Region	QUIN concentration (nmol/g wet weight) Moroni[a] ($n = 8$)	QUIN concentration (nmol/g wet weight) Wolfensberger[b] ($n = 6$)	QPRT specific activity[c] (fmol NAMN·h^{-1}·mg tissue^{-1}) ($n = 6$)
Olfactory bulb	—	—	47.73±3.23
Cortex	2.10±0.2	1.58±0.27	2.22±0.15
Striatum	0.60±0.1	0.759±0.29	2.50±0.55
Hippocampus	1.00±0.2	—	2.93±0.27
Thalamus	0.85±0.2	—	8.99±0.95
Hypothalamus			16.68±2.43
Cerebellum	0.90±0.1	0.434±0.64	4.01±0.45
Brain stem	0.90±0.2	—	8.45±0.77
Spinal cord	—	—	4.69±0.67

NOTE: Values are means ± SEM. NAMN, nicotinic acid mononucleotide.
[a]Moroni, Lombardi: et al. 1984.
[b]Wolfensberger et al. 1983.
[c]Foster, Zinkand et al. 1985.

similar to those of IBO which acts as an agonist at this receptor site (Watkins and Evans 1981). Indeed, some of the neurotoxic actions of QUIN resemble those of IBO; focal injections of QUIN do not result in lesions distal to the injection site (Kohler et al. 1979; Guldin and Markowitsch 1981), and the neurotoxic effects of QUIN can be blocked by agents that selectively antagonize IBO such as the aminophosphonates (Schwarcz, Whetsell, and Foster 1983). However, QUIN toxicity also resembles that induced by KA in that QUIN neurotoxicity is dependent on the presence of intact excitatory amino acid afferents (Schwarcz et al. 1984), there is a regional distribution of toxicity (Schwarcz and Kohler 1983), and QUIN does not produce toxicity in immature animals (Schwarcz et al. 1984). However, QUIN has a low affinity for the KA receptor (Schwarcz et al. 1984), suggesting QUIN toxicity is not associated with KA receptor activation.

To determine if receptor activation is related to neurotoxicity, a large number of compounds including QUIN have been tested for their ability to release [^{3}H]ACh from striatal slices and produce lesions of striatal neurons (Lehmann et al. 1985). Dipicolinic acid (2,6-pyridine dicarboxylic acid), a QUIN analogue, was as potent and efficacious as QUIN in releasing [^{3}H]ACh from striatal slices; however, this compound apparently does not produce neurotoxic lesions (Lehmann et al. 1985). It has been proposed by Schwarcz et al. (1984) that the neurotoxic effect of QUIN involves interaction with a presynaptic receptor leading to the release of an endogenous substance such as glutamic acid; however, interaction with a postsynaptic receptor can not be excluded. Rothman (1985) has recently suggested that the neurotoxicity produced by glutamate, *N*-methyl-D-aspartate and kainate is mediated by an influx of chloride ions into the neuron.

Regional distribution of neurotoxicity

The neurotoxicity of QUIN shows a regional sensitivity in the rat brain. Based on a morphological study, the striatum, pallidal formation and hippocampus were most susceptible to QUIN toxicity; whereas the cerebellum, substantia nigra, amygdala, medial septum, and hypothalamus were more resistant (Schwarcz and Kohler 1983. It is important to note that cholinergic neurons in the nucleus basalis magnocellularis (NBM) are vulnerable to the toxic actions of QUIN (Schwarcz and Kohler 1983); El-Defrawy, Coloma et al. 1985), while similar neurons in the medial septum are less sensitive. The cholinergic neurons of the rostral column located in the medial septum, nucleus of the diagonal band and NBM are thought to form a continuum of neurons that project via cholinergic afferents to the hippocampus, cerebral cortex, amygdala, and olfactory bulb (Mesulam et al. 1983; Satoh et al. 1983). Thus, there appears to be a gradient in the sensitivity of these cells to QUIN with the anteriodorsal portion (Medial septum) showing low and the posterioventral portion (NBM) showing high sensitivity. It is possible that the gradient in sensitivity to QUIN is a direct result of a gradient in glutamatergic or aspartergic afferent innervation to these areas.

TABLE 2. Choline acetyltransferase (CAT) activity in rat cortex or striatum following quinolinic acid (QUIN) lesions of the nucleus basalis magnocellularis (NBM) or striatum, respectively

QUIN (nmol)	% decrease in cortical CAT[a] following QUIN injection into NBM[b] (mean ± SEM, $n = 4$–9)	% decrease in striatal CAT[a] following QUIN injection into NBM[c]
Sham	12.3±2.4	
60	9.6±5.3	4.0
90	22.5±5.2	
120	55.1±1.3	
150	57.3±9.1	22.0
200	59.0±5.7	
300	—	50.0

[a]Data represent the percent decrease in CAT activity from the lesioned hemisphere when compared with the contralateral control hemisphere.
[b]Adapted from Boegman et al. 1984; Boegman et al. 1985.
[c]Adapted from Schwarcz, Whetsell, and Mangano et al. 1983.

Injections of QUIN into the NBM result in a dose-dependent reduction of the presynaptic cortical cholinergic markers: acetylcholinesterase (AChE), high affinity choline uptake (HACU), potassium (K^+)-evoked [^{3}H]ACh release, and choline acetyltransferase (CAT) (Table 2) (Boegman et al. 1984, 1985; El-Defrawy, Coloma et al. 1985). Schwarcz, Whetsell, and Mangano (1983) found that striatal cholinergic markers are

TABLE 3. Potassium (35 m*M*) evoked release of [^{3}H]acetylcholine (ACh) from rat cortical slices following lesions of the nucleus basalis magnocellularis (NBM) with quinolinic acid (120 nmol)[a]

Time (weeks)	% decrease in [^{3}H]ACh release[b] (mean ± SEM, n = 3–8)
1 (sham)	10.0±3.5
1	40.7±7.8
3	37.0±4.3
6	31.8±8.2
12	44.5±8.8

[a]Data from El-Defrawy, Jhamandas et al. 1985; El-Defrawy, Boegman et al. 1985; Jhamandas et al. 1985.
[b]Data represent the percent decrease in [^{3}H]ACh release from the cortex of the lesioned hemisphere when compared with the contralateral control cortex.

reduced following intrastriatal administration of QUIN (Table 2); however, the dose required was more than double that used in the NBM to produce a similar reduction in CAT (Table 2) (Boegman et al. 1985). Injections of kainic acid or ibotenic acid into the NBM have been reported to reduce cortical cholinergic function (Lehmann et al. 1980; Johnston et al. 1979, 1981; El-Defrawy, Coloma et al. 1985; Bartus et al. 1985). However, following excitotoxic lesions of the NBM, cortical markers of GABAergic, noradrenergic, histaminergic, and serotonergic neurons remain unchanged (Johnston et al. 1981). We observed no evidence of recovery in cholinergic markers in the frontoparietal cortex following injections of IBO or QUIN into the NBM during a 12-week period (Table 3) (El-Defrawy, Jhamandas et al. 1985; El-Defrawy, Boegman et al. 1985; Jhamandas et al. 1985). In addition, Bartus et al. (1985) failed to find recovery in cortical CAT and HACU 6 months after an IBO lesion of the NBM. In contrast, a study has reported complete recovery of cortical CAT and HACU 3 months following an injection of IBO into the NBM (Wenk and Olton 1984).

Because maximal lesions of the NBM induced by neurotoxins produce only a 60–70% reduction in cortical cholinergic markers, it was suggested that the cortex received cholinergic innervation from other sources (Lehmann et al. 1980). Johnston and co-workers (1981) found that intracortical injections of KA resulted in a 30% reduction in cortical CAT activity, suggesting intrinsic cortical cholinergic innervation. However, using intracortical QUIN injections (300 nmol), El-Defrawy, Coloma et al. (1985) failed to observe depletion of cortical cholinergic markers, including K^+-evoked release of [^{3}H]acetylcholine. Similar results were obtained by Lehmann et al. (1980) and El-Defrawy, Coloma et al. (1985) using intracortical KA injections. The presence of cholinergic neurons intrinsic to the cortex has recently been demonstrated by immunohistochemical techniques (Eckenstein and Thoenen 1983; Houser et al. 1985).

Kynurenic acid antagonism

An important aspect of the kynurenine pathway is that kynurenine (Fig. 1) not only serves as the precursor of QUIN, but may also be converted to another intermediate, kynurenic acid (KYN) (Brown 1980). KYN acts as an antagonist of certain excitatory amino acids including QUIN (Perkins and Stone 1982; Ganong et al. 1983). Using microiontophoretic techniques, Perkins and Stone (1982) were the first to demonstrate that KYN was a potent antagonist of QUIN, NMDA, and quisqualic acid. In the hippocampus, KYN antagonized both the seizures and neurodegeneration precipitated by local injection of QUIN (Foster, Vezzani et al. 1984), while in the striatum, KYN prevented QUIN-induced cell death and afforded complete protection against QUIN-induced decreases in CAT activity (Foster, Vezzani et al. 1984). We have found that, in the NBM, KYN was also able to offer complete protection against QUIN-induced neurodegeneration and subsequent decreases in cortical cholinergic markers, including [^{3}H]ACh release. A KYN:QUIN molar ratio of 0.35:1 resulted in a 50% protection of cortical CAT activity, while complete protection was obtained at an equimolar ratio (Table 4) (Boegman et al. 1984, 1985). This supports previous observations that KYN protects against QUIN-induced neurotoxicity *in vivo* (Table 2) (Foster, Vezzani et al. 1984). Injections of KYN alone into the NBM were without effect on cortical cholinergic markers, suggesting that KYN does not act as a partial agonist. This is in agreement with electrophysiological data showing KYN to have no effect on spontaneous activity of cortical neurons (Perkins and Stone 1982).

TABLE 4. Choline acetyltransferase activity in rat cortex or striatum following coinjections of quinolinic acid (QUIN) and kynurenic acid (KYN) in different molar ratios

KYN:QUIN (molar ratio)	% decrease in cortical CAT[c] following injection into the NBM[d] (mean ± SEM, n = 4–9)	% decrease in striatal CAT[c] following injection into the striatum[e] (mean ± SEM, n = 5)
0:1[a]	55.1±1.3	48.8±3.4
0.25:1[a]	36.3±14.6	
0.42:1[b]		48.8±11.0
0.5:1[a]	19.3±11.2	
0.67:1[b]		26.84±16.0
0.83:1[b]		11.22±6.0
1:1[a]	8.0±5.1	
4.42:1[b]		2.93±6.0

[a]QUIN dose remained constant at 120 nmol.
[b]QUIN dose remained constant at 240 nmol.
[c]Data represent the percent decrease in CAT activity from the lesioned hemisphere when compared with the contralateral control hemisphere.
[d]Data from Boegman et al. 1984; Boegman et al. 1985.
[e]Data from Foster, Vezzani et al. 1984.

TABLE 5. Pharmacological agents aimed at improving cholinergic function

Effect	Agent	Mechanism (proposed)
Increase synthesis of ACh	Choline	Increase availability of choline[a]
	Carbohydrates	Increase availability of acetyl CoA[b]
Increase presynaptic ACh release	Adrenocorticotrophic hormone	Modulation of neuronal firing[c]
	Naloxone	Blockade of inhibitory input[d,e]
	Aminopyridines	Prolong action potential[f,g,h,i,j]
	Nootropics	Increase metabolic rate[k,l,m]
	Methylxanthines	Block inhibitory adenosine modulation[n,o]
	Somatostatin	Enhance ACh turnover[p,q]
	TRH	
	Angiotensin II	
Blockade of presynaptic muscarinic receptors	Presynaptic muscarinic antagonists	Prevent autoinhibition
Potentiation of postsynaptic action	AChE inhibitors	Prolong ACh synaptic life[r]
	Direct acting cholinergic agonists	Direct postsynaptic activation[s]
	VIP	Potentiate postsynaptic effect of ACh[t]
Promote regeneration or sprouting	Gangliosides[u,v]	
	Neuronotrophic factors[w]	
Cell transplant	Fetal cells[x,y]	

[a]Reviewed by Blusztajn and Wurtman, 1983.
[b]Growdon and Wurtman 1983.
[c]Botticelli and Wurtman 1981.
[d]Jhamandas et al. 1977.
[e]Jhamandas and Sutak 1983.
[f]Wesseling et al. 1984.
[g]Peterson and Gibson 1983.
[h]Thesleff 1980.
[i]Matsumoto and Riker 1983.
[j]Doleza land Tucek 1983.
[k]Giurgea 1982.
[l]Bartus et al. 1981.
[m]Gallagher et al. 1983.
[n]Pedata, Pepeu et al. 1984.
[o]Harms et al. 1979.
[p]Malte-Sorenssen et al. 1978.
[q]McGeer 1984.
[r]Thal et al. 1983.
[s]Harbaugh et al. 1984.
[t]Lundberg et al. 1982.
[u]Pedata, Giovannelli et al. 1984.
[v]Toffano et al. 1984.
[w]Schonfeld et al. 1985.
[x]Segal et al. 1985.
[y]Isaacson et al. 1984.

While the presence of KYN has not been demonstrated in the brain, kynurenine, the immediate precursor of KYN, and kynurenine transaminase, the enzyme converting kynurenine to KYN, have both been detected in cerebral tissue (Minatogawa et al. 1974; Gal and Sherman 1978). This evidence suggests the presence of KYN in the CNS. Thus, as suggested by Schwarcz et al. (1984), an imbalance in the tryptophan metabolic pathway leading to a change in the ratio of agonist (QUIN) to antagonist (KYN) might have some relevance to the etiology of neurodegenerative disease.

Implication of QUIN lesions in the NBM

Impairment of cortical cholinergic function, due to loss of neurons in the nucleus basalis of Meynert, has been observed in Alzheimer's disease (reviewed by McGeer, 1984). This lack of cholinergic function could be a contributing factor to the progressive deterioration of cognitive function associated with this disease. Thus, animals with QUIN-induced lesions of the NBM, showing sustained deficits in cholinergic markers may be useful models for testing pharmacological treatments aimed at improving both cortical cholinergic function and behaviour. Certain pharmacological strategies proposed by a number of different authors that may be used to improve the release of acetylcholine are summarized in Table 5. It should be noted that animals with neurotoxin-induced lesions of the NBM do not show neuritic plaques, tangled neurofilaments or alterations in other neurotransmitter systems as has been reported in Alzheimer's disease (McGeer 1984).

Acknowledgements

The authors acknowledge the financial support of the Ontario Mental Health Foundation and the Canadian Geriatric Research Society. We thank Ms. L. Shipton for technical assistance and Ms. J. LeSarge for typing the manuscript.

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