The 1993 Upjohn Award Lecture. Quinolinic acid induced brain neurotransmitter deficits: modulation by endogenous excitotoxin antagonists

K.H. JHAMANDAS[1] AND R.J. BOEGMAN
Department of Pharmacology and Toxicology, Queen's University, Kingston, ON K7L 3N6, Canada

AND

R.J. BENINGER
Department of Psychology, Queen's University, Kingston, ON K7L 3N6, Canada

Received August 17, 1994

JHAMANDAS, K.H., BOEGMAN, R.J., and BENINGER, R.J. 1994. The 1993 Upjohn Award Lecture. Quinolinic acid induced brain neurotransmitter deficits: modulation by endogenous excitotoxin antagonists. Can. J. Physiol. Pharmacol. **72**: 1473–1482.

Excitotoxins constitute a group of agents that are capable of activating excitatory amino acid receptors and producing axon-sparing neuronal lesions. Focal injections of the exogenous excitotoxins kainic acid and ibotenic acid result in depletion of neurotransmitter markers in neuronal cell bodies located in areas of injection or in terminal zones of their projections. The discovery of endogenous agents that behave as excitotoxins has generated interest in the idea that excitotoxicity may contribute to the neuronal degeneration associated with a number of neurological diseases (Alzheimer's disease, Huntington's disease, Parkinson's disease) which involve selective neurotransmitter deficits. Quinolinic acid (QUIN), a pyridine dicarboxylic acid and metabolite of tryptophan, which has been detected in the central nervous system (CNS), behaves as an excitotoxin. In the mammalian brain QUIN has been localized to glial and immune cells, and its content increases with age. The neuroexcitatory and neurotoxic actions of QUIN are mediated via the Mg^{2+}-sensitive *N*-methyl-D-aspartate (NMDA) receptor. The toxicity of QUIN, like that of kainate, but not ibotenate, is dependent on the presence of an intact glutamate–aspartate afferent input to the target area. Focal injections of QUIN into the nucleus basalis magnocellularis (nbM), a major source of cholinergic innervation to diencephalic areas, produce sustained loss of cholinergic neuron markers in the neocortex and amygdala. The neurotoxic action of QUIN on nbM results in an impairment of performance on memory-related tasks. Cortical and amygdaloid projecting cholinergic neurons show differential sensitivity to QUIN and other excitotoxic agents. This factor may partly explain the reported discrepancy between mnemonic deficits and the loss of cholinergic markers in the cerebral cortex induced by intra-nbM injections of certain excitotoxins. Cortical muscarinic receptor function is not significantly influenced by QUIN injections into the nbM producing loss of cortical cholinergic neurons. In the striatum, focal QUIN injections have been found to largely replicate the neurotransmitter deficits prevailing in Huntington's disease, an inherited movement disorder. Intrastriatal QUIN produces a profound loss of the NADPH diaphorase staining neurons in the area of injection but relatively spares these in the adjacent transition zone. QUIN is also highly damaging to the striatopallidal enkephalinergic neurons. However, at doses that are neurotoxic to striatal neurons, QUIN and several other excitotoxins produce significant elevations in enkephalin levels both in the striatum and globus pallidus. This elevation reflects the presence of a plasticity in the striatal enkephalinergic neuron population. The metabolic pathway yielding QUIN produces a number of intermediates that act as excitotoxin antagonists. Kynurenic acid, the most potent of these endogenous agents, blocks the action of QUIN and other excitotoxins that act on NMDA and non-NMDA receptors. Picolinic acid, a pyridine monocarboxylic acid, also attenuates QUIN toxicity. However, it only influences excitotoxins that require an intact glutamatergic afferent input to the target area for the expression of their neurotoxic action. Although picolinic acid modulates presynaptic glutamate release in vitro, this action does not entirely explain its restricted anti-excitotoxic action. The presence of several endogenous excitotoxin antagonists in the CNS has important implications for neuron survival. A balance between endogenous excitotoxins and their built-in antagonists may influence the viability of neuronal groups in the CNS. It also suggests a novel strategy for influencing excitotoxicity through elevations in levels of endogenous antagonists. Nicotinylalanine, an enzyme inhibitor, elevates brain kynurenate levels and exhibits potential for anticonvulsant and anti-excitotoxic action. The study of QUIN and related agents holds promise of understanding factors that underlie neuronal damage and developing novel agents to reduce or prevent this damage in areas of the CNS affected in neurodegenerative disease.

Key words: quinolinic acid, brain, neurotransmitters, deficits, excitotoxin, antagonists.

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Les exictotoxines forment un groupe de substances capables d'activer les récepteurs des acides aminés excitateurs et de provoquer des lésions neuronales sans endommager les axones. Des injections focales des excitotoxines exogènes, acide kaïnique et acide iboténique, provoquent une diminution des marqueurs de neurotransmetteurs dans les corps cellulaires localisés dans les aires d'injection ou dans les terminaisons de leurs projections. La découverte de substances endogènes ayant les mêmes propriétés que les excitotoxines a amené à considérer l'idée que l'excitotoxicité pourrait contribuer à la dégénérescence neuronale associée à plusieurs maladies neurologiques (maladie d'Alzheimer, maladie de Huntingdon, maladie de Parkinson) qui impliquent des déficits de neurotransmetteurs sélectifs. L'acide quinolinique (QUIN), un acide dicarboxylique de la pyridine et métabolite du tryptophane, qui a été détecté dans le système nerveux central (SNC), agit comme une excitotoxine. Dans le cerveau de mammifère, QUIN a été localisé dans les cellules immunes et gliales, et sa concentration augmente

[1]Author for correspondence.

Printed in Canada / Imprimé au Canada

avec l'âge. Les actions neurotoxiques et neuroexcitatrices de QUIN sont transmises par le récepteur d'acide *N*-méthyl-D-aspartique (NMDA) sensible au Mg^{2+}. La toxicité de QUIN, comme celle du kaïnate mais pas de l'iboténate, dépend de la présence d'une projection afférente glutamate−aspartate intacte à la région cible. Des injections focales de QUIN dans le nucleus basalis magnocellularis (nbM), une source majeure d'innervation cholinergique des aires diencéphaliques, induisent une perte continue de marqueurs neuronaux cholinergiques dans le néocortex et l'amygdale. L'action neurotoxique de QUIN sur le nbM altère la performance des tâches liées à la mémoire. Les neurones cholinergiques des projections amygdaliennes et corticales présentent une sensibilité différente à QUIN et aux autres agents excitotoxiques. Ce facteur pourrait expliquer en partie la dissociation entre les déficits mneumoniques et la perte de marqueurs cholinergiques dans le cortex cérébral, induite par des injections intra-nbM de certaines excitotoxines. La fonction des récepteurs muscariniques corticaux n'est pas significativement influencée par les injections nbM de QUIN induisant une perte de neurones cholinergiques corticaux. Dans le striatum, des injections focales de QUIN ont reproduit dans une large mesure les déficits de neurotransmetteurs prédominant dans la maladie de Huntingdon, un trouble moteur héréditaire. Le QUIN intrastriatal détruit considérablement les neurones associés à la NADPH diaphorase dans la région d'injection, mais épargne jusqu'à un certain point ceux situés dans la zone de transition adjacente. QUIN altère aussi grandement les neurones enképhalinergiques striato-pallidaux. Toutefois, aux doses neurotoxiques pour les neurones striataux, QUIN et plusieurs autres excitotoxines entraînent des augmentations significatives des taux d'enképhaline tant dans le striatum que dans le globus pallidus. Cette augmentation reflète la présence d'une plasticité dans la population de neurones enképhalinergiques striataux. La voie métabolique menant à QUIN crée plusieurs sous-produits qui se comportent comme des antagonistes des excitotoxines. L'acide kynurénique, le plus puissant de ces agents endogènes, bloque l'action de QUIN et des autres excitotoxines qui agissent sur les récepteurs non NMDA et NMDA. L'acide picolinique, un acide monocarboxylique de la pyridine, atténue aussi la toxicité de QUIN. Toutefois, il n'influe que sur les excitotoxines nécessitant une projection afférente glutamatergique intacte à la zone cible pour exprimer leur action neurotoxique. Bien que l'acide picolinique module la libération de glutamate présynaptique in vitro, cette action n'explique pas entièrement son action anti-excitatrice limitée. La présence de plusieurs antagonistes endogènes des excitotoxines dans le SNC a d'importantes conséquences pour la survie neuronale. Un équilibre entre les excitotoxines endogènes et leurs antagonistes naturels pourrait influencer la viabilité des groupes neuronaux dans le SNC. Elle suggère aussi une stratégie nouvelle pour influer sur l'excitotoxicité, soit par l'augmentation des taux d'antagonistes endogènes. La nicotinylalanine, comme inhibiteur enzymatique, augmente les taux de kynurénate dans le cerveau et présente un potentiel d'action antiexcitotoxique et anticonvulsivant. L'étude de QUIN et des substances qui lui sont apparentées devrait permettre de mieux comprendre les facteurs sous-jacents à l'altération neuronale et de développer de nouveaux agents pour réduire ou prévenir ces lésions dans les régions du SNC touchées par les maladies neurodégénératives.

Mots clés : acide quinolinique, cerveau, neurotransmetteurs, déficits, excitotoxine, antagonistes.

[Traduit par la Rédaction]

Introduction

In 1954, Hayashi provided the first description of neuroactive properties of L-glutamic acid (L-Glu). Three years later, Lucas and Newhouse (1957) demonstrated the neurotoxic potential of L-Glu on retinal neurons of infant mice. These pioneering discoveries opened an era of research on excitatory amino acids (EAAs), which has established that dicarboxylic acids, such as L-Glu and L-aspartate (L-Asp), act as major excitatory synaptic transmitters in the mammalian central nervous system (CNS), and that excitation produced by these substances can lead to neuronal death. Olney's early experiments showing damaging actions of L-Glu and L-Asp on the brain in infant animals led to the proposal that these agents may act as excitotoxins, producing neuronal depolarization to the point of ionic overload and irreversible cell damage (Olney and Ho 1970; Olney 1978, 1990). The concept of excitotoxicity and its implications for neuronal death in the CNS became a subject of major interest following animal studies (Coyle and Schwarcz 1976; McGeer and McGeer 1976) showing that injections of kainic acid into the rat striatum replicate the neurochemical pathology of Huntington's disease (HD), an autosomal dominant neurodegenerative disease involving a severe depletion of striatal neuron populations and impairments of cognitive and motor function (Martin and Gusella 1986). These and numerous other studies on excitotoxin-induced neuronal damage have heightened interest in the idea that certain environmental or endogenous substances may act as excitotoxins to produce specific neuronal loss (Table 1), which characterizes neurodegenerative disorders such as senile dementia of Alzheimer's type (SDAT), HD, Parkinson's disease (PD), and other CNS disorders involving progressive neuron loss. Excitotoxicity has also been implicated in acute brain damage associated with hypoxia−ischemia (Simon et al. 1984; Rothman and Olney 1986), hypoglycemia (Auer et al. 1985; Weiloch 1985), and sustained seizure activity (Clifford et al. 1989).

Several years of experimental research on excitotoxins has revealed that activation of all major ionotropic EAA receptors (*N*-methyl-D-asparate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), kainate) can produce neuronal damage (Choi 1988). Studies on isolated neuronal tissue and neuronal cultures have identified an initial rapid phase of damage involving translocation of Na^+ and Cl^-, and a slower phase involving Ca^{2+} influx (Rothman 1985; Choi 1985; Garthwaite and Garthwaite 1986; Olney et al. 1986). More recently, nitric oxide (NO), a gaseous messenger molecule, has been implicated as an intermediary in the NMDA receptor mediated functions, including neurotoxicity (Dawson et al. 1991).

The ability of exogenous agents such as kainate and ibotenate to cause profound neuronal damage raised the possibility that certain endogenous agents in the CNS may mimic their effects in the CNS and thus behave as endogenous excitotoxins. The idea of endogenous excitotoxins gained credence following the discovery of the neurotoxic properties of quinolinic acid (QUIN) (Schwarcz et al. 1983), a pyridine dicarboxylic acid yielded by the metabolism of tryptophan via the kynurenine pathway (Brown 1980). QUIN, which acts as an NMDA receptor agonist, has been implicated in the pathogenesis of chronic neurodegenerative diseases, most notably HD. More recently, QUIN has been implicated in the neuronal pathology associated with brain inflammatory disease, including that associated with acquired immunodeficiency syndrome (AIDS) (Heyes 1993).

In experimental studies, QUIN has been used to produce models of regional neurotransmitter deficits that mimic the features of neuronal pathology seen in human neurodegenerative diseases. These models of focal neuronal damage have yielded a wealth of information on factors influencing cell damage, including the relationships between neurochemical and behavioural deficits. The focus of our research effort in this area has involved study of the action of QUIN and related excitotoxins on brain cholinergic and noncholinergic neurons and modulation of this action by endogenous antagonists. This research is based on the premise that excitation-based models of neurotransmitter deficits can provide insight into the etiology of human neurodegenerative diseases and contribute to therapeutic treatments for such diseases.

Origin of QUIN

QUIN ((pyridine 2,3-dicarboxylic) acid) is an intermediate in the metabolism of tryptophan via the kynurenine pathway (Fig. 1), which is much more active in the periphery than the brain (Gal and Sherman 1978, 1980; Speciale and Schwarcz 1993). The presence of enzymes responsible for QUIN synthesis (3-hydroxyanthranilic acid oxygenase (3-HAO)) and QUIN degradation (quinolinic acid phosphoribosyl transferase (QPRT)) has been demonstrated in brain tissue. The levels of activity of these enzymes vary in different brain regions (Foster et al. 1985*a*, 1985*b*; Wolfensberger et al. 1983). QUIN itself is widely distributed in the mammalian brain, the highest levels being present in the cerebral cortex and hippocampus (Moroni et al. 1984*a*). However, extracellular QUIN, unlike L-Glu, does not appear to undergo reuptake or metabolism. Moroni et al. (1984*a*) showed that QUIN, although derived from the same precursor as 5-hydroxytryptamine (5-HT), is not located in neuronal elements that contain this indoleamine, since 5,7-dihydroxytryptamine, a neurotoxin that depletes 5-HT stores, fails to influence QUIN levels in the rat brain. The brain levels of QUIN show an increase with age (Moroni et al. 1984*b*).

Although earlier brain studies have implied a localization of QUIN to neurons, recent studies have pointed to an extraneuronal localization of this dicarboxylic acid. Immunocytochemical studies involving enzyme histochemistry have shown that 3-HAO and QPRT are localized in glial cells (Schwarcz 1993). However, a recent immunocytochemical study, involving use of a polyclonal antibody against QUIN, failed to detect QUIN in glial cells but localized it to immune cells (Moffett et al. 1993). Heyes et al. (1988*a*) showed that immune stimulation results in augmented levels of QUIN in the brain. Human patients with viral infections, including the human immunodeficiency virus (HIV-I), show markedly elevated levels of QUIN in the cerebrospinal fluid (Heyes et al. 1989). These and other findings have led to the proposal that QUIN and related products of tryptophan metabolism may be involved in the brain pathology accompanying neuroinflammatory conditions. Recently, QUIN has been implicated in the pathophysiology of brain ischemia. Delayed elevations in QUIN have been observed in gerbil brain following transient ischemia (Heyes and Nowak 1990).

Excitotoxic action of QUIN

The first description of neuroactive properties of QUIN was provided by Lapin (1978, 1982), who demonstrated its convulsant action in rodents. Subsequently, both electrophysiological (Stone and Perkins 1981; Perkins and Stone 1982) and neurochemical studies (Lehmann et al. 1983) identified QUIN as an agonist at the NMDA receptor. In 1983, Schwarcz et al. reported that a focal application of QUIN to the rat striatum produced a marked depletion of striatal cholinergic neurons. Subsequent studies in the striatum showed that intrastriatal injection of QUIN in the rat replicates the amino acid transmitter and neuropeptide deficits that prevail in the brain of patients with HD (Beal et al. 1986). Thus, QUIN has been employed to produce models of neurochemical deficits in different brain regions, including the basal forebrain, an area implicated in the cortical cholinergic pathology associated with SDAT (see below).

TABLE 1. Major neurotransmitter deficits in some neurodegenerative diseases

Disease	Pathway	Neurotransmitter
Alzheimer's	Basocortical	Acetylcholine[a]
	Cortical	Somatostatin[b]
Parkinson's	Nigrostriatal	Dopamine[c]
Huntington's	Striatopallidal	GABA, enkephalin[d]
	Striatonigral	Substance P,[d] GABA[e]

[a]Davies and Maloney 1976.
[b]Davies et al. 1980.
[c]Hornykiewicz 1966.
[d]Emson et al. 1980.
[e]Perry et al. 1973.

The neurotoxic action of QUIN, like that of ibotenic acid and NMDA, is initiated via activation of NMDA receptors (Schwarcz et al. 1984). Electrophysiological and receptor binding studies conducted over the past few years have produced evidence for NMDA receptor heterogeneity (Ffrench-Mullen et al. 1986; Peet et al. 1986; Burton et al. 1988; Monaghan et al. 1988). Recent molecular studies have further revealed the existence of several subtypes of NMDA receptors and non-NMDA receptors, including multiple metabotropic receptors (Nakanishi 1992). It has been suggested that the excitatory and neurotoxic actions of QUIN may be mediated by a receptor subtype that differs from that activated by ibotenic acid or NMDA (Winn et al. 1991). However, experiments on compounds structurally related to QUIN have revealed that excitatory actions seen in vitro are dissociable from the excitotoxic action of these agents observed in vivo (Lehmann et al. 1985). The in vivo excitotoxic response is dependent not only on the initial depolarization of target neurons bearing EAA receptors but, in the case of some excitotoxins, the expression of this response is dependent on the presence of an intact presynaptic EAA input to the region of excitotoxin injection. QUIN and kainic acid, although activating distinct EAA receptors, represent excitotoxins that are only neurotoxic in the presence of an intact EAA innervation to the target neurons (Köhler et al. 1978; McGeer et al. 1978; Schwarcz et al. 1984). Unlike the action of QUIN, however, the excitotoxicity of ibotenate or NMDA does not appear to be dependent on an intact afferent input (Steiner et al. 1984; Silverstein et al. 1986). This factor may have an important bearing on the regional and neuronal differences in the neurotoxic action of QUIN or in the action of EAA antagonists on QUIN toxicity (Schwarcz and Köhler 1983; Dunnett et al. 1987; Winn et al. 1991; Boegman et al. 1992).

In the striatum, the glutamatergic innervation from the cortex to this area significantly influences the neurotoxicity of QUIN and kainic acid. In the absence of the corticostriatal pathway

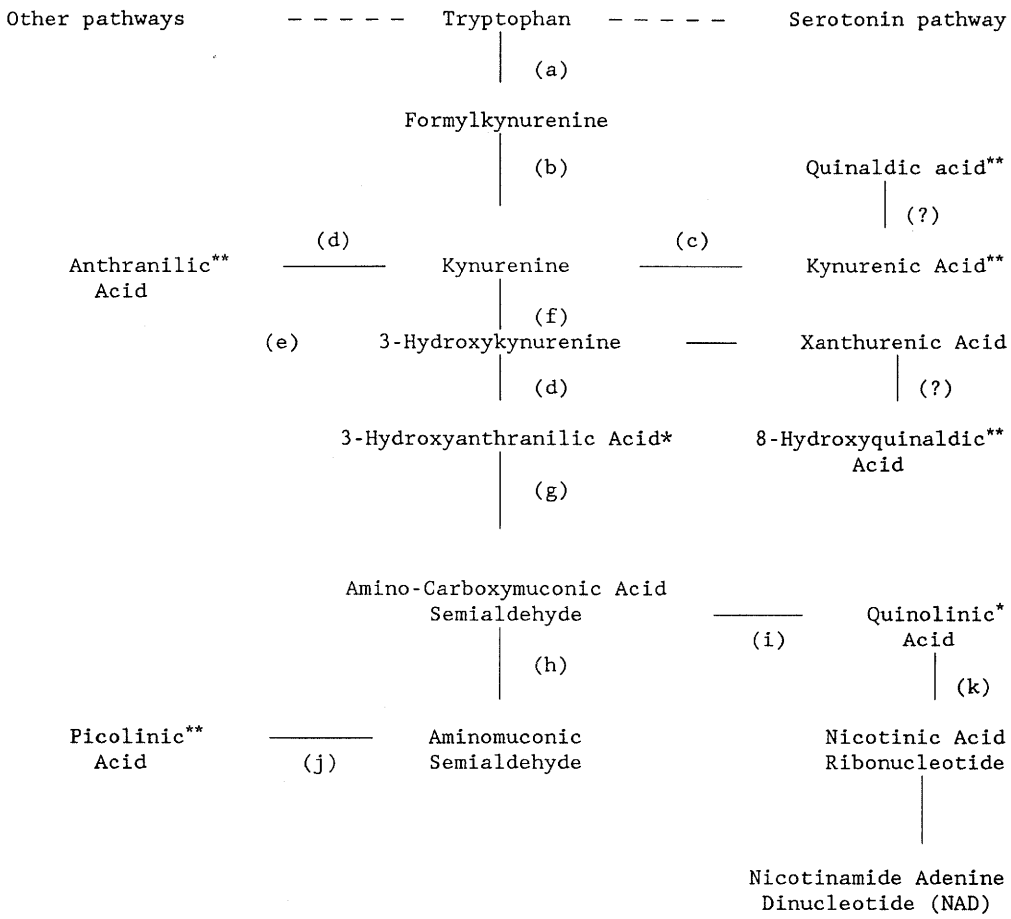

FIG. 1. Scheme of tryptophan metabolism via kynurenine pathway showing some major metabolites. *a*, tryptophan 2,3-dioxygenase and (or) indoleamine 2,3-dioxygenase; *b*, formamidase; *c*, kynurenine aminotransferase; *d*, kynureninase; *e*, anthranilic acid 3-hydroxylase; *f*, kynurenine 3-hydroxylase; *g*, 3-hydroxyanthranilic acid oxygenase; *h*, picolinate carboxylase; *i*, nonenzymatic (?); *j*, nonenzymatic (?); *k*, quinolinic acid phosphoribosyltransferase. *neurotoxic; **antineurotoxic (Jhamandas et al. 1990).

striatal neurons are much less sensitive to QUIN or kainate neurotoxicity (Campochiaro and Coyle 1978; Galarraga et al. 1990). In contrast, striatal neurons lacking glutamatergic innervation are highly sensitive to the action of NMDA (McDonald and Johnston 1990). The permissive role of glutamatergic innervation in QUIN toxicity has implications for neuronal degeneration in the striatum and possibly other brain areas. It is possible that in neurological disease states alterations in function of the glutamatergic afferents may render certain striatal neurons vulnerable to concentrations of endogenous QUIN that normally are not toxic to these neurons.

The requirement of presynaptic EAA afferents for the production of excitotoxicity suggests that the release of an EAA transmitter from these afferents may be critical for the expression of toxicity. In several studies kainic acid has been reported to produce a receptor-mediated EAA release in vitro and in vivo (Ferkany et al. 1982; Collins et al. 1983; Young et al. 1988; Vrooman et al. 1993), and an excitatory action of QUIN on EAA release has been demonstrated in the cortex (Connick and Stone 1988) and the striatum (Fedele and Foster 1993). However, in brain regions that have been deprived of presynaptic EAA input and consequently have become unresponsive to some neurotoxins, co-injection of the EAA transmitter fails to restore the neurotoxic action to the level seen in the presence of this input (Biziere and Coyle 1979). Thus, presynaptic factors other than the release of EAA neurotransmitter have an influence on the excitotoxic response. Such factors may include the divalent cation zinc, which has recently been found to be released by the EAAs (Badar-Goffer et al. 1994).

QUIN action on basal forebrain cholinergic neurons

Large neurons located in the basal forebrain nuclei (medial septum, diagonal band of Broca, and nucleus basalis magnocellularis (nbM)) provide major cholinergic innervation to the hippocampus, neocortex, and amygdala (Mesulam et al. 1983). These forebrain areas show a severe depletion of cholinergic markers in SDAT (Davies and Maloney 1976; Bowen et al. 1982). Infusions of QUIN into the rat nbM produce dose-related depletion of biochemical markers of cholinergic neurotransmission in the neocortex (El-Defrawy et al. 1985). The depletion of high affinity choline uptake (HACU) is preceded by a transient but significant increase in this marker, reflecting an initial excitation of the nbM cholinergic neurons (Metcalf et al. 1987). This activation of HACU is also reflected in an increased cortical binding of hemicholinium-3, a specific inhibitor of HACU, which has been used as a label for the sodium-dependent choline transporter (Rainbow et al. 1984; Vickroy et al. 1985). The reduction in all four presynaptic cholinergic markers (cholineacetyltransferase (ChAT) activity, acetylcholinesterase (AChE) activity, HACU, and [^{3}H]acetylcholine (ACh) release) is sustained over a 3-month period following a single QUIN

injection into the nbM, signifying sustained damage to the neuronal projection from nbM to the cortex (El-Defrawy et al. 1986). The decrease in presynaptic cortical [^{3}H]ACh release parallels the reduced release of this transmitter from cortical tissue obtained from brains of patients with SDAT (Sims et al. 1983). However, the QUIN-induced lesions of the nbM were found not to produce changes in cortical muscarinic receptor function, as assessed by measurement of carbachol-stimulated phosphotidylinositol turnover in cortical slices (Scarth et al. 1989). Although the functional status of muscarinic receptors in SDAT is unclear, it has been reported that in this condition the M_1 muscarinic receptor (postsynaptic) binding remains unaltered, while M_2 receptor (presynaptic) binding is significantly reduced (Mash et al. 1985). Thus at a biochemical level, intra-nbM injections of QUIN faithfully reproduce the cortical cholinergic deficits that are apparent in SDAT.

Excitotoxic lesions of the nbM have been reported to also produce certain behavioural deficits reflecting a dysfunction of memory (Coyle et al. 1983; Hepler et al. 1985; Dunnett et al. 1987). Unilateral injections of QUIN into the nbM, at doses producing significant cortical but not hippocampal cholinergic damage, have been found to produce greater impairment of the working than reference memory-related tasks in radial maze task (Wirsching et al. 1989). As the animals showing mnemonic deficits are those that also exhibit a marked reduction in cortical cholinergic markers, the behavioural impairments in such animals appear to be due to the loss of cholinergic neuron projections from nbM to the cortex.

It has been suggested by some investigators that memory-related impairments may result from damage to unidentified noncholinergic neurons in the nbM (Dunnett et al. 1991). This suggestion is derived from experimental studies showing that excitotoxins producing the greatest reduction in cortical ChAT activity do not produce the greatest deficits in memory-related tasks (Wenk et al. 1989; Markowska et al. 1990; Connor et al. 1991). However, anatomical studies have shown that cholinergic projections from the nbM neurons do not exclusively project to the neocortex and that nbM neurons also send significant projections to the amygdala (Emson et al. 1979; Mesulam et al. 1983; Heckers and Mesulam 1994). The amygdala region has been implicated in memory processes (Sarter and Markowitsch 1985) and appears to receive cholinergic projections from a distinct population of nbM neurons. A recent study comparing the action of several excitotoxins on the nbM revealed that there are important differences between these agents with respect to their ability to destroy cortical or amygdaloid cholinergic projections following focal injections (Boegman et al. 1992). The rank order of potency of those excitotoxins that differ in their ability to produce mnemonic deficits is indeed different in regard to their action on cortical and amygdaloid cholinergic projections. Thus, a differential action of excitotoxin injections on the two cholinergic pathways may be an important factor in the discrepancy observed between cortical ChAT loss and memory impairments. The reasons for the differences in the vulnerability of distinct nbM cholinergic neurons to excitotoxins are not known. However, potential differences in distribution of EAA receptors on these neurons or in their innervation by EAA afferents may be important factors in this regard.

In attempts to achieve a highly selective depletion of the cholinergic pathways originating from nbM, the actions of phthalic acid (1,2-benzene dicarboxylate), an agent previously reported to activate cortical (Stone 1984) and striatal (Lehmann et al. 1985) neurons, were evaluated following its focal nbM injections. Phthalate produced a very large decrease in amygdaloid but not cortical ChAT activity, and the injected animals showed a selective impairment of working memory in maze experiments (Mallet et al. 1995). Thus, cholinergic projections to the amygdala appear to play an important role in mnemonic functioning. This conclusion is reinforced by the observation that injections of the muscarinic antagonist scopolamine into the amygdala also produce significant mnemonic deficits (Ingels et al. 1993). However, the comparative roles of cortical and amygdaloid projecting nbM neurons, and indeed of hippocampal cholinergic projections, in various aspects of the memory process remain to be studied. In regard to the sensitivity of the hippocampal cholinergic neurons to QUIN, experiments involving injection of this excitotoxin into the diagonal band – medial septum have shown that such injections produce a modest decrease in ChAT activity compared with the large decrease that is seen in the cortex or amygdala following the intra-nbM injections (K.H. Jhamandas and J. Cockhill, unpublished results). While this may suggest a reduced sensitivity of the hippocampal projection to QUIN, the lesser effect of QUIN is most likely attributable to the difficulty of exposing a relatively large tissue region to the focally administered excitotoxin.

QUIN action on striatal neurons

Excitotoxins, including QUIN, have been extensively used in experimental studies to model the neurochemical deficits associated with HD, which is characterized by loss of the medium-sized spiny neurons. Thus, intrastriatal QUIN has been found to produce loss of neurons containing GABA, substance P, enkephalin, and dynorphin (neurotransmitters that are severely depleted in HD) in both rodents (Beal et al. 1986) and nonhuman primates (Ferrante et al. 1993). However, the effects of intrastriatal QUIN on other neurotransmitters, somatostatin and neuropeptide Y (NPY), which are associated with the NADPH diaphorase (NADPH-d) neurons and are relatively spared in HD (Dawbarn et al. 1985; Albin et al. 1990), are controversial. Whereas some investigators have reported a relative sparing of these neurons following QUIN injections (Beal et al. 1986), others have reported a high sensitivity of these neurons to this excitotoxin (Boegman et al. 1987; Davies and Roberts 1987). Recently, a study of excitotoxin action on the pattern of NADPH-d and enkephalin neuron survival following intrastriatal QUIN and kainate injections has revealed that methodological differences in evaluation of the neurotoxic response may underlie the controversial findings (Roberts et al. 1993). According to that study, QUIN does not produce absolute sparing of NADPH-d neurons in the lesion core, but spares these neurons in an adjacent area, which has been labelled the transition zone.

HD involves a substantial loss of enkephalin and substance P containing striatopallidal and striatonigral neurons, which can precede the onset of clinical symptoms of the disease (Reiner et al. 1988). Striatal injections of excitotoxins, including QUIN, have been found to produce a depletion of enkephalin-immunoreactive neurons (Schwarcz et al. 1980; Beal et al. 1991; Roberts et al. 1993). However, biochemical measurements of methionine enkephalin (Met-Enk) levels in the QUIN-lesioned striata have revealed an elevation rather than a decrease in enkephalin levels (Hong et al. 1980; Ruzicka and Jhamandas 1990). This elevation of Met-Enk in the striatum following a unilateral injection is also produced by other excitotoxins, shows a specific time course, and is bilateral (Ruzicka and

Jhamandas 1990; Ruzicka et al. 1991). The post-QUIN increase in enkephalin levels, which occurs at a time period at which the striatal enkephalin neurons are depleted (as reflected in the decreased levels of preproenkephalin mRNA), is suggestive of an intrinsic plasticity in the striatal enkephalin neuron population. Hong et al. (1980) have suggested a role for enkephalins in the seizures provoked by activation of certain EAA receptors. Thus, enhanced opioid levels may have a role in the modulation of seizures or neuronal damage initiated by focal excitotoxin injections (Kanamatsu et al. 1986). In the striatum, enkephalins have been shown to reduce presynaptic release of the corticostriatal transmitter (L-Glu or L-Asp) and to hyperpolarize striatal neurons (Jiang and North 1992). Thus, enkephalin, and possibly other endogenous opioids, may modulate excitotoxin-induced damage to striatal neurons through a pre- and post-synaptic inhibitory action.

Although the excitotoxin-induced elevations in enkephalin levels may appear to be inconsistent with the observation of enkephalin neuron depletion in HD, they are consistent with a report of elevated striatal Met-Enk immunoreactivity in a human subject showing pathology of the striatum without clinical symptoms of chorea (Schiffmann and Vanderhaeghen 1989).

Modulation of QUIN excitotoxicity by endogenous antagonists

One of the most intriguing aspects of QUIN pharmacology is that QUIN is derived from a metabolic pathway that also yields kynurenic acid and several other intermediates that block QUIN-induced excitotoxic damage (Fig. 1). Kynurenic acid acts as an anti-excitatory agent, blocking QUIN action on neuronal firing (Perkins and Stone 1982), and as anti-excitotoxic agent, blocking QUIN-induced neuronal damage (Foster et al. 1984). In the nbM model of cholinergic neurotoxicity, kynurenic acid was found to fully block the QUIN-induced loss of cortical cholinergic markers (Boegman et al. 1985) and prevent the mnemonic deficits arising from loss of nbM neurons (Wirsching et al. 1989). The anti-excitatory and anti-excitotoxic actions of kynurenic acid most likely arise from a blockade of the strychnine-insensitive glycine site associated with the NMDA receptor (Kessler et al. 1989). The anti-excitotoxic action of kynurenic acid is shared by several other intermediates (e.g., quinaldic acid and picolinic acid), although none of these agents is as potent as kynurenate (Jhamandas et al. 1990). However, quinaldic acid and picolinic acid, which appear not to interact with the strychnine-insensitive glycine site (Kessler et al. 1989), must exert their anti-excitotoxic action by a different mechanism.

Picolinic acid, a pyridine monocarboxylic acid originating from the precursor that yields QUIN, a pyridine dicarboxylic acid, is of interest since it appears to exert an anti-excitotoxic action without producing a significant impairment of synaptic transmission. In hippocampal slices, picolinic acid, unlike kynurenic acid, does not significantly influence the synaptically driven electrical responses (Robinson et al. 1985). However, picolinic acid affords protection against QUIN-induced damage to the nbM cholinergic neurons (Cockhill et al. 1992), the nigrostriatal dopaminergic neurons (Beninger et al. 1994), and striatal NADPH-d neurons (Kalisch et al. 1993). The anti-excitotoxic action of picolinic has a certain structural and excitotoxin selectivity. Studies in the nbM model of neurotoxicity have shown that focally injected picolinic acid attenuates the neurotoxic action of excitotoxins (QUIN, kainic acid) that require an intact glutamatergic afferent input for the expression of their neurotoxicity, but not that of agents (ibotenate and quisqualic acid) that lack this requirement. This suggests that picolinic acid may act by modulating the afferent glutamatergic input at a presynaptic level, possibly by influencing the release of transmitter. In striatal slice experiments, picolinic acid has been found to inhibit the calcium-dependent release of L-Glu produced by kainic acid (Vrooman et al. 1993). However, this effect does not entirely explain the anti-excitotoxic action of picolinic acid, since the picolinate analogues nicotinic acid and isonicotinic acid do not show a similar structural selectivity in regard to their anti-release and anti-excitotoxic actions (Vrooman et al. 1993). Picolinic acid is known to chelate zinc (Suzuki et al. 1957), and recently it has been found to influence the NO pathway in activated macrophages (Melillo et al. 1993, 1994). Zinc has been shown to interact with the NMDA receptor, which incorporates a binding site for this cation. NO, a gaseous messenger molecule, has been implicated in NMDA receptor mediated responses (Garthwaite 1991). Thus, it is possible that the antitoxic effect of picolinic acid involves a zinc- and (or) NO-based mechanism of action.

The ability of kynurenic acid and other tryptophan metabolites to act as EAA antagonists provides a basis for modulation of excitatory synaptic function or excitotoxicity through elevations in CNS levels of these endogenous antagonists. In 1978, Gal and Sherman showed that administration of radiolabelled tryptophan indeed leads to the appearance of labelled kynurenate and quinaldic acid in the rat brain. Moroni and colleagues (1988) have shown that the content of endogenous kynurenate in the brain can be measured, shows regional variability, and can be increased by tryptophan loading or by probenecid, an agent that blocks organic acid transport from brain to the circulation. Kynurenic acid can be liberated in the extracellular fluid following administration of its immediate precursor kynurenine, and this efflux can be blocked by inhibition of kynurenine aminotransferase (KAT), and enzyme catalyzing conversion of the precursor to kynurenic acid (Turski et al. 1989; Speciale et al. 1990; Swartz et al. 1990). The production of kynurenic acid in the CNS appears to occur in glial cells (astrocytes), possibly in those processes that contain the enzyme KAT and that surround neurons (Du et al. 1992). Thus, this anatomically specific location of the enzyme favours modulation of neuronal activity by the liberated kynurenic acid and possibly other related agents.

Recently, it has become possible to elevate brain kynurenate levels through the use of nicotinylalanine (Nicala), an inhibitor of kynureninase and kynurenine hydroxylase, which was originally used by Decker et al. (1963) in studies of tryptophan metabolism. Russi et al. (1992) have reported that Nicala treatment reduces endotoxin-induced accumulation of QUIN and enhances the accumulation of kynurenic acid in the brain. In experimental animals, Nicala prevents chemically induced seizures, an effect that has been attributed to elevation of brain kynurenic acid (Connick et al. 1992). We have examined the potential of Nicala to prevent excitotoxin-induced damage in the CNS and have found that systemic or central administration of this agent, when coupled with kynurenine and probenecid treatment, prevents QUIN-induced damage to the striatal NADPH-d neurons at a dose elevating brain kynurenate level (Harris et al. 1993). In the protection experiments involving Nicala, the precursor kynurenine is administered to serve as a source for kynurenic acid and the latter is prevented from leaving the brain by an injection of probenecid. It remains to be seen whether

pharmacologically relevant elevations in brain kynurenate can be achieved by enzyme inhibitors in the absence of adjunct treatments. Such agents, if developed, would have the potential to act as neuroprotectants.

The unique aspect of QUIN metabolism and pharmacology provides opportunities for development of neuroactive agents with potential to mimic the actions of endogenous antagonists, block the production of QUIN, or elevate brain levels of endogenous antagonists. Thus, in the past few years there has been the discovery of pharmacological agents with this potential. Chlorokynurenic acid, an analogue of kynurenic acid, is a more potent and selective ligand at the NMDA receptor linked glycine site (Kemp et al. 1988). The agent 4-chloro-3-hydroxyanthrailic acid, an analogue of the QUIN precursor 3-hydroxyanthrailic acid, blocks the synthesis of QUIN (Heyes et al. 1988*b*; Todd et al. 1989; Speciale and Schwarcz 1993). Nicala, an analogue of kynurenine, inhibits the enzyme kynurenine hydroxylase and elevates brain levels of kynurenic acid (Russi et al. 1992). These and other specific agents that are likely to follow in the future can be used as tools to explore further the role of QUIN in neuropathological phenomena and to develop novel pharmacological agents with therapeutic potential.

Concluding remarks

The discovery of the excitotoxic property of QUIN has lent credence to the idea that endogenous excitotoxins may have a role in the pathophysiology of neurological disorders that involve neuron damage or death. Its ability to destroy several different neuron populations through activation of NMDA receptors in the presence of an intact glutamatergic afferent input suggests that QUIN may be an important mediator of cell death in the CNS. However, its role in human neurodegenerative disease is far from established. Clinical studies have failed to show augmented levels of QUIN in the brain or cerebrospinal fluid of patients with neurodegenerative diseases (Moroni et al. 1986; Schwarcz et al. 1988; Heyes et al. 1991), although elevated QUIN levels have been observed in neuroinflammatory disorders (Heyes 1993). However, considering that production of QUIN from tryptophan is associated with that of metabolites that antagonize its excitotoxic action, a balance between the levels of QUIN and these endogenous antagonists may be more important than the level of agonist alone. Data in this regard are sparse, but a clinical study has suggested that in HD there is reduced formation of kynurenic acid (Beal et al. 1990). Thus, while the role of endogenous antagonists in neurological disease remains to be explored, changes in levels of these antagonists could influence neuron survival in the CNS. However, a complicating factor in this regard is that at high doses the endogenous antagonists themselves can behave as agonists (Kudo and Ogura 1986; Ruzicka and Jhamandas 1990) and thus have the potential to contribute to neuronal pathology (Rieke 1992).

Acknowledgements

The authors acknowledge the financial support of the Ontario Mental Health Foundation, the Medical Research Council of Canada, Parkinson's Foundation of Canada, Gerontological Research Council of Ontario, and Queen's University. Contributions from graduate students, research assistants, and research collaborators are very gratefully acknowledged. The authors thank Ms. Bernice Ison for assistance in preparing the manuscript.

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