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Neurotoxins and Neurotoxic Species Implicated in Neurodegeneration

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Neurotoxins, in the general sense, represent novel chemical structures which when administered *in vivo* or *in vitro*, are capable of producing neuronal damage or neurodegeneration - with some degree of specificity relating to neuronal phenotype or populations of neurons with specific characteristics (*i.e.*, receptor type, ion channel type, astrocyte-dependence, etc.). The broader term 'neurotoxin' includes this categorization but extends the term to include intra- or extracellular mediators involved in the neurodegenerative event, including necrotic and apoptotic factors. Moreover, as it is recognized that astrocytes are essential supportive satellite cells for neurons, and because damage to these cells ultimately affects neuronal function, the term 'neurotoxin' might reasonably be extended to include those chemical species which also adversely affect astrocytes. This review is intended to highlight developments that have occurred in the field of 'neurotoxins' during the past 5 years, including MPTP/MPP$^+$, 6-hydroxydopamine (6-OHDA), methamphetamine; salsolinol; leukoaminochrome-*o*-semiquinone; rotenone; iron; paraquat; HPP$^+$; veratridine; soman; glutamate; kainate; 3-nitropropionic acid; peroxynitrite anion; and metals (copper, manganese, lead, mercury). Neurotoxins represent tools to help elucidate intra- and extra-cellular processes involved in neuronal necrosis and apoptosis, so that drugs can be developed towards targets that interrupt the processes leading towards neuronal death.

Keywords: Neurotoxins; Neurodegeneration; Necrosis; Apoptosis; MPTP; 6-OHDA; Methamphetamine; Rotenone; Leukoaminochrome-*o*-semiquinone; Salsolinol; Paraquat; Veratridine; Peroxynitrite anion; 3-Nitropropionic acid; Soman; Glutamate; Kainate; Domoate; MPP$^+$; HPP$^+$; Iron; Copper; Manganese; Lead; Mercury

INTRODUCTION

In the inaugural issue of the journal *Neurotoxicity Research*, a synopsis of commonly used neurotoxins was provided, and several other implicated neurotoxic species were highlighted (Kostrzewa, 1999). On this 5th anniversary we again focus on still-actively studied neurotoxins, and identify other chemicals and metabolites that have since been recognized as having an active role in promoting necrosis, apoptosis, and ultimately the neurodegenerative process. This compendium is not intended to be comprehensive, rather the puropose is to recognize chemical species which are in the forefront of **Neurotoxicity Research**. This paper is intended to be a vanguard for reviews that will be published in this journal during the next several years, each with a focus on species outlined here; or reviews on newly discovered neurotoxic species. Already two of these reviews have been published in 2004 in *Neurotoxicity Research* - one by Chandrasankar *et al.* (2004) on domoic acid; and another, in this issue, by Baumgarten and Lachenmayer (2004) on serotoninergic neurotoxins - in which the mechanisms of 5,6-dihydroxytryptamine (5,6-DHT) and 5,7-DHT are discussed, along with the actions of substituted amphetamines.

Although there are hundreds, maybe thousands, of compounds that will produced (nerve) cell death when applied in abnormally high amount, the term 'neurotoxin' generally implies specificity of action on a particular cellular component, when given in relative small amount - either acutely or chronically. Because astrocytes and microglia have prominent, even essential roles in supporting function and viability of neurons, it is reasonable to now expand the term 'neurotoxin' to include those compounds that have relatively selective deleterious effects on the neuronal satellite cells.

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Following, is a brief summary of action of actively widely studied neurotoxins and neurotoxic species, as well as a description of novel research directions with these chemical species.

MONOAMINERGIC NEUROTOXINS

MPTP

In the last 5 years there were more than 950 papers published on MPTP; altogether, 3300 papers were published on 'MPTP' since its discovery [The term 'MPTP' was entered in PUB MED].

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a selective dopaminergic pro-neurotoxin that crosses the blood-brain barrier, and is then accumulated by astrocytes and converted by monoamine oxidase-B (MAO-B) in the astrocytes to MPP^+ (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium ion), the active neurotoxic metabolite of MPTP. MPP^+, having selective affinity for the dopamine (DA) transporter (DAT), is largely accumulated in DA nerves - which accounts for MPTP selectivity for DA nerves. Inside the nerve MPP^+ inhibits the mitochondrial respiratory chain (mainly a complex I inhibitor), which thereby interferes with energy production which adversely affects cellular function, leading to disruption in Ca^{2+} homeostasis and further adverse effects that lead to the neurotoxicity. MPTP produces irreversible Parkinson syndrome in primates including humans. When given systemically, MPTP primarily destroys nigrostriatal DA nerve endings; if administered in pars compacta substantia nigra (SN), MPTP does destroy DA cell bodies. In MPTP-treated primates and black mice, but not in albino rats, these anatomical lesions are associated with loss of tyrosine hydroxylase, reduction in the DAT number, and a decrease in DA content (see Mytilineou, 2001).

Chronic administration of MPTP produces a dose-dependent decrease in striatal DA concentration, and a corresponding loss of striatal vesicular monoamine transporter (VMAT-2) protein in wild-type mice (Drolet *et al.*, 2004; Xu *et al.*, 2004). The MPTP-treated primate responds to the administration of L-DOPA and other antiparkinsonian drugs providing a model to study the mechanism of dopaminergic degeneration, to test new drugs and studies on locomotor activity (Jenner and Marsden, 1986; Gerlach *et al.* 1991; Archer *et al.*, 2003).

There are a number of recent and novel aspects relating to MPTP. Because the toxic effect of MPP^+ is potentiated by dicoumarol-induced inhibition of the enzyme DT-diaphorase, it appears that DA oxidation to aminochrome is a major mechanism by which MPP^+ exerts toxicity (Aguilar Hernandez *et al.*, 2003). Also, hydroxyl radical ($HO^{\cdot}$) is a likely mediator of MPTP/MPP^+, since acetyl-L-carnitine attenuates neurotoxicity by reducing $HO^{\cdot}$ as well as xanthine oxidase-generated uric acid (Loots *et al.*, 2004); and the free radical scavenger green tea polyphenol (-)-epigallocatechin-3-gallate protects from *in vitro* neurotoxicity of MPTP/MPP^+ (Mandel *et al.*, 2003). Moreover, Wang *et al.* (2004) show that the Jun-N-terminal kinase (JNK) pathway is a major mediator of the MPTP-induced neurotoxicity. Using assorted JNK-deficient mice, Hunot *et al.* (2004) show that both JNK2 and JNK3 are required for MPTP-induced c-Jun activation and dopaminergic cell demise, and that cyclooxygenase (COX) 2 is the molecular target of JNK activation. Significantly, Vaglini *et al.* (2004) find that the cytochrome P450 2E1 apparently has a detoxifying (neuroprotective) role, as inhibitors of this enzyme potentiate MPTP neurotoxicity. These series of recent studies signal the importance of generated or prevented reactive oxygen species (ROS) as neurotoxic and neurprotective avenues.

The presence of active microglia in the SN pars compacta (pcSN) of three patients who had been exposed to MPTP several years before death suggested a role of inflammation in the neurotoxic action of MPTP (Barcia *et al.*, 2003). Even more recently, it has been found (with IL-18 knockout mice) that MPTP activates microglial cells via IL-18 (interleukin-18) and that the activated microglia promote loss of SN dopaminergic cells (Sugama *et al.*, 2004). In a similar vein, MPTP was found to activate microglia and induce the expression of macrophage antigen complex-1 (MAC-1) (Ferger *et al.*, 2004) and S-100 protein (Kato *et al.*, 2004) by microglia, while arundic acid-suppression of S-100 expression was neuroprotective against MPTP (Kato *et al.*, 2004) as was the TNF-alpha suppression (in knockout mice and in thalidomide treated mice) (Ferger *et al.*, 2004). These findings implicate microglia as prominent mediators of neurotoxicity.

There were two major and recent findings with MPTP toxicity, relating potentially to prevention and treatment of Parkinsons's disease (PD). In the first study the adoptive transfer of copolymer-1 immune cells to MPTP-treated mice was associated with T cell accumulation in pcSN, suppression of microglial activation, increased local expression of glial cell line-derived neurotrophic factor, protection from MPTP-induced cell loss of DA neurons in pcSN, and attenuation of DA denervation in striatum. These findings give credence to the potential of therapeutic immunization as a treat-

ment strategy for PD (Benner *et al.*, 2004). The other major finding is that viral transfer of the chaperone heat-shock protein 70 (Hsp70) [or sonic hedgehog] gene to DA neurons by a an adeno-associated virus inhibited MPTP-induced neurodegenerative loss of DA neurons (after MPTP or 6-OHDA) and attenuated DA denervation of rodent striatum (Dass *et al.*, 2004; Dong *et al.*, 2005). This finding indicates the potential of viral transfer of genes as a preventive or as a means for slowing the progression of neurodegenerative disorders.

Paraquat

The herbicide 1,1'-dimethyl-4,4'-bipyridium (paraquat) has been suggested to induce parkinsonism based both on reports of parkinsonism correlated with exposure to the agent (Hertzman *et al.*,1990; Liou *et al.*,1997) and its structural similarity to the active metabolite of MPTP, namely MPP^+ (Schneider and Denaro, 1988). The uptake of paraquat into the CNS is mediated via the blood-brain barrier neutral amino acid transporter (McCormack and Di Monte, 2003). Paraquat generates superoxide both through electron transfer reactions with NADH-dependent oxidoreductases and by redox cycling via reaction with molecular oxygen (for review, see Andersen, 2003) Paraquat is known to produce oxidative stress both in neurons and astroglia (Schmuck *et al.*, 2002), and its selectively toxicity to dopaminergic neurons of the SN (McCormack *et al.*, 2002) can be prevented by estradiol, a sex hormone with anti-oxidant properties (Gelinas *et al.*, 2004).

6-Hydroxydopamine (6-OHDA)

In the last 5 years there were more than 1250 papers published on 6-OHDA; altogether, 6000 papers were published on '6-OHDA' since its discovery [The term '6-hydroxydopamine' was entered in PUB MED].

Originally discovered as the first highly selective neurotoxin - for catecholaminergic neurons - in the late 1960s (Tranzer and Thoenen, 1967), 6-OHDA has proven to be a useful chemical tool 1) for producing neurodegeneration, 2) for subseqent dilineation of cellular mechanisms involved in neurotoxicity, 3) for identification of cellular processes that can be activated to preserve neuronal function and viability, 4) for definition of (neurotrophic) factors involved in regeneration of partially damaged (axotimized) nerves, 5) for discernment of the vital role of satellite cells in promoting recovery from damage, 6) for definition of the process of neurogenesis subsequent to damage to a neuropil, and 7) for recognition of the compensatory mechanisms that phenotypically different types of neurons undergo after damage to a single nerve phenotype.

Recent reviews have been written on 6-OHDA, some focused on lesions in adulthood (see Zigmond and Keefe, 1998), some focused on lesions in ontogeny (see Breese and Breese, 1998), some focused specifically on mechanisms of action (see Blank, 1998; Kostrzewa *et al.*, 1998; Kostrzewa, 2001; Kostrzewa and Segura-Aguilar, 2003).

6-OHDA owes it selectivity of action to the fact that it has high affinity to the norepinephrine (NE) transporter and DA transporter. Accordingly, 6-OHDA is accumulated in toxic amounts in NE and DA nerves, thereby damaging them. If damage is 'slight', nerve terminals are primarily lost; if damage is 'moderate', axotomy is produced; if damage is great, perikarya undergo necrosis or apoptosis. By co-administering a NE transport inhibitor (*e.g.*, desipramine) simultaneous with 6-OHDA, then damage is largely restricted to only dopaminergic nerves. A long-useful model for studying parkinsonian disorders is the unilateral 6-OHDA-lesioned rat (*i.e.*, 6-OHDA directly into substantia nigra to destroy perikarya; or 6-OHDA directly into striatum to damage to DA innervation). These rats circle in the direction of the lesion, while DA agonists produce contralateral turning - owing to development of D_2 receptor supersensitization on the lesioned side (Ungerstedt, 1971; Costall *et al.*, 1975; Marshall and Ungerstedt, 1977; Berger *et al.*, 1990; Archer *et al.*, 2003).

Toxicity of 6-OHDA is related to the production of reactive oxygen species (ROS) including superoxide radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and of hydroxyl radical ($HO^{\cdot}$) (Cohen and Heikkila, 1974; Cohen *et al.*, 1976), as well as catechol-*O*-quinones (Solano *et al.*, 2000). 6-Hydroxydopamine causes death of dopaminergic neurons by mitochondrial dysfunction with c-Jun N-terminal kinases as central mediators (Eminel *et al.*, 2004). The toxicity of 6-hydroxydopamine is attenuated in transgenic mice that overexpress bcl-2 (Offen *et al.*, 1998). Today, the major focus for studies related to 6-OHDA is largely into mechanisms associated with pro- and anti-apoptotic factors. A secondary focus is related to DA receptor supersensitivity that develops after the lesion, persisting throughout the lifespan (Kostrzewa, 1995; Brus *et al.*, 2003; Kostrzewa *et al.*, 2003; 2004).

Rotenone

Rotenone is a well characterized and commonly used inhibitor of complex I of the mitochondrial respiratory chain and induces selective destruction of nigral

dopaminergic neurones in rats. However, it is also a herbicide commonly used by gardeners as the active ingredient of derris dust or liquid preparations of derris described as 'natural herbicide', which are commonly found on the shelves of garden centres. Because it is extremely lipophilic, it crosses biological membranes easily and independent of transporters (unlike MPP^+), and enters the brain very rapidly (Talpade *et al.*, 2000). Rotenone toxicity is thought to be mediated, in part, by DA *per se*, since a superoxide dismutase mimetic and alpha-methyl-*p*-tyrosine (synthesis-inhibitor) attenuate toxicity (Sakka *et al.*, 2003). Rotenone-dependent dopaminergic degeneration is accompanied by a marked increase in oxidative protein damage (carbonyls) in dopaminergic brain regions. Behaviorally, rotenone-infused animals developed symptoms of parkinsonism, including bradykinesia and rigidity. Severely affected rats also developed the flexed posture and motor 'freezing' typical of advanced PD. Thus, chronic, systemic rotenone infusion recapitulated the anatomical, biochemical, pathological and behavioral features of PD (for review, see Greenamyre *et al.*, 2003; Uversky, 2004). However, it must be recognized that other brain regions are vulnerable to rotenone toxicity, including the hippocampal CA1 region (Xu *et al.*, 2003).

Leukoaminochrome-*o*-semiquinone

Neurotoxicity induced by DA or L-DOPA is thought to occur, not only as adverse actions of long-term L-DOPA therapy, but also in the pathogenesis of PD. Numerous *in vitro* and *in vivo* studies demonstrate the ability of DA and L-DOPA to produce neurotoxicity and apoptosis in a plethora of different cell lines (Ziv *et al.*, 1994; Offen *et al.*, 1995; 2001; Cheng *et al.*, 1996; Masserano *et al.*, 1996; 2000; Simantov *et al.*, 1996; Lai and Yu, 1997; Velez-Pardo *et al.*, 1997; Cadet and Brannock, 1998; Jacobsson and Fowler, 1999; Asanuma *et al.*, 2003; Emdadul *et al.*, 2003). The ortho-phenolic groups of DA and L-DOPA play a crucial role in their toxicity. Within nerve vesicles, DA is in high concentration but virtually unreactive because of the low pH which keeps the phenolic groups well protonated. However, within the cytoplasm proper, at physiological pH, DA can dissociate and be oxidized by free oxygen to DA-*o*-quinone, which spontaneously cyclizes in several steps to aminochrome. DA oxidation to aminochrome is also catalyzed by enzymatic routes (prostaglandin H synthase, cytochrome P450 isoforms, xanthine oxidase, tyrosinase, dopamine monooxygenase [MAO]) and non-enzymatic routes (transitional metals) (Hawley *et al.*, 1967; Graham, 1978¸ Segura-Aguilar and Lind, 1989; Hastings, 1995; Segura-Aguilar, 1996; Foppoli *et al.*, 1997; Terland *et al.*, 1997; Galzigna *et al.*, 2000; Thompson *et al.*, 2000; Paris *et al.*, 2001; 2005; Smythies *et al.*, 2002; Bustamante *et al.*, 2004). Saturation of DA uptake into vesicles and MAO metabolism allows intracellular DA autoxidation to aminochrome, which in turn is the precursor of neuromelanin in dopaminergic neurons. It has been reported that neuromelanin synthesis is abolished by adenoviral-mediated over-expression of the synaptic vesicle catecholamine transporter VMAT2, which would decrease cytosolic DA by increasing vesicular accumulation of the neurotransmitter (Sulzer *et al.*, 2000). Oxidation of DA to aminochrome and its polymerization to neuromelanine seems to be a normal and non toxic pathway but under certain conditions aminochrome can be reduced by one electron to leukoaminochrome-*o*-semiquinone radical, which is extremely reactive with oxygen, autoxidizing with the generation of a redox cycling between two reactions (aminochrome + NADH/NADPH --> leukoaminochrome *o*-semiquinone radical and leukoaminochrome *o*-semiquinone radical + O_2 --> aminochrome + $O_2^{\cdot-}$) (Baez *et al.*, 1995; Segura-Aguilar *et al.*, 1998). This redox cycling is initiated by one-electron reduction of aminochrome, catalyzed by flavoenzymes using NADH or NADPH, and is extremely rapid and potent, producing acute neurotoxicity. This redox cycling results in (i) the depletion of NADH, which is required for ATP synthesis in the mitochondria; (ii) depletion of NADPH, which is required to maintain glutathione (GSSG/GSH) in the reduced state (GSH) - necessary for its exerting antioxidant actions; (iii) depletion of oxygen, required for ATP synthesis in the mitochondria; (iv) formation of $O_2^{\cdot-}$, which spontaneously or enzymatically generate H_2O_2, the precursor of $HO^{\cdot}$. Highly neurotoxic in cells *in vitro*, leucoaminochrome-*o*-semiquinone radical has been proposed as a endogenous neurotoxin in rats, capable of inducing neurodegeneration of dopaminergic neurons (Paris *et al.*, 2001; 2005; Segura-Aguilar *et al.*, 2002; Arriagada *et al.*, 2004; Diaz-Veliz *et al.*, 2004a). One of the target proteins for DA *o*-quinone is thought to be α-synuclein, which is a major component of insoluble fibrils of Lewy bodies in PD (Conway *et al.*, 2001).The soluble state of α-synuclein is converted to aggregated fibrils via transient formation of pathogenic protofibrils by its oligomerization. It was found that DA oxidation inhibits the formation of fibrils since DA quinone reacted with α-synuclein to form the DA *o*-quinone-α-synuclein adduct, stabilizing the protofibrils (Conway *et al.*, 2001).

Salsolinol

Among catechol isoquinolines, NM(*R*)salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, Sal), naturally occurring in brain, is the most cytotoxic to DA neurons (Vetulani *et al.*, 2003), causing behavioral, histopathological and biochemical changes in the nigro-striatum, which are quite similar to those observed in parkinsonian patients (Naoi *et al.*, 1996; 1998). Sal has been detected in the urine of parkinsonian patients treated with L-DOPA (Sandler *et al.*, 1973; Maruyama *et al.*, 1996), and the level of NM(*R*)Sal in the CSF of parkinsonian patients was significantly higher *vs* control (Moser and Kompf, 1992; Moser *et al.*, 1995). After 1 week of repeated injections of NM(*R*)Sal into the striatum, the number of DA neurons stained with anti-TH antibody was reduced markedly in the SN, but a necrotic reaction was not observed, suggesting that NM(*R*)Sal caused apoptotic cell death selectively in DA neurons of the rat model. Sselective neurotoxicity of salsolinol purportedly is dependent on its selective uptake through the DA transporter, followed by DA oxidation to quinone methide, and its subsequent one-electron reduction to sequinone radical (Martinez-Alvarado *et al.*, 2001). Inhibition of DT-diaphorase potentiates the *in vivo* neurotoxic effect of intranigral injection of salsolinol (Diaz-Veliz *et al.*, 2004a).

Methamphetamine

Methamphetamine (METH) is an illicit drug of abuse that produces degeneration of dopaminergic systems (Cadet *et al.*, 1994). Although the cellular and molecular events involved in METH-induced neurotoxicity remains to be elucidated there is a generally accepted role for oxygen radicals in the neurotoxic actions of this drug (Cadet, 2001). The administration of METH is associated with a toxic cascade that involves the production of $O_2^{\cdot-}$, H_2O_2 and $HO^{\cdot}$ as well as quinone production (LaVoie and Hastings, 1999). In transgenic mice that express much higher CuZn-SOD activity than wild-type animals from similar backgrounds, the toxic effects of METH were significantly attenuated in a gene dosage fashion, with homozygous mice showing greater protection (Hirata *et al.*, 1996). Although it has been suggested that $HO^{\cdot}$ are derived from DA metabolism following METH administration, it was recently shown that METH administration via an *in vivo* microdialysis probe (in rat striatum) did not generate $HO^{\cdot}$ (Pereira *et al.*, 2004).

METH-induced glutamate overflow has been proposed as the mediator of METH toxicity, glutamate antagonists afford neuroprotection from METH (Sonsalla *et al.*, 1989; O'Dell *et al.*, 1994). The mGluR5 receptor appears to have the closest association in mediation of METH effects (see Baumgarten and Lachenmayer, 2004). A role for NO in the toxic effects of METH is supported by the recent observation that the toxic effect of METH on dopaminergic markers was attenuated in nNOS knockout mice (Itzhak *et al.*, 1998). The protein p53 seems to play an important role in METH-induced neurotoxicity, since animals lacking the gene for the p53 protein were protected against METH neurotoxicity (Hirata and Cadet, 1997). Kappa-opioid receptor agonists do not protect against METH-induced toxicity to monoaminergic neurons in rats, and may potentiate mortality when co-administered with METH (Johnson-Davis *et al.*, 2003).

NMDA RECEPTOR-RELATED NEUROTOXINS

Glutamate

L-Glutamate (glutamate), the major excitatory neurotransmitter in brain, is also categorized as an excitotoxin. Activation of the NMDA (rNMDA) and AMPA (rAMPA) subtypes of ionotropic glutamate receptors is a necessary event for the acquisition of several types of memory (Cammarota *et al.*, 2004; Igaz *et al.*, 2004; Izquierdo *et al.*, 2004). Extracellular glutamate levels are elevated following ischemia, hypoglycemia, and trauma. Glutamate is known to be involved in the pathophysiology of neuronal cell death in hypoxic-ischemic brain injury (Schousboe and Frandsen, 1995) and other neurodegenerative disorders (Greenamyre and Young, 1989; Perry and Hansen, 1990; Rothstein *et al.*, 1995). Neurotoxicity can be prevented with NMDA receptor antagonists (see Dave *et al.*, 2003b).

Glutamate cytotoxicity occurs largely from the resulting intracellular increase in ROS (Boldyrev *et al.*, 2004). Excessive release of glutamate from neural cells is observed after brain damage, and the consequent over-activation of glutamate receptors results in necrotic and apoptotic neuronal death (Jacobsson and Fowler, 1999; Tapia *et al.*, 1999) and cell swelling, primarily in astrocytes (Kimelberg, 1995; Han *et al.*, 2004). Glutamate toxicity is the major contributor to pathological cell death within the central nervous system. There are two forms of glutamate toxicity:

(i) Receptor-initiated excitotoxicity. Overstimulation of glutamate receptors likely induces the intracellular accumulation of several substances, including Ca^{2+}, Na^{+}, inositol-1,4,5-trisphosphate, and diacylglycerol.

Blockade of this induction might be accomplished most easily by antagonizing postsynaptic glutamate receptors, but also might be accomplished by reducing glutamate release from presynaptic terminals, or improving glutamate clearance from synaptic clefts (for review see Choi, 1990).

(ii) Nonreceptor-mediated toxicity. Reactive oxygen species in cell death caused by oxidative glutamate toxicity was studied in an immortalized mouse hippocampal cell line HT22. An initial 5-10-fold increase in ROS after glutamate addition is temporally correlated with GSH depletion. This early increase is followed by an explosive burst of ROS production to 200-400-fold above control values. The source of this burst is the mitochondrial electron transport chain, while only 5-10% of the maximum ROS production is caused by GSH depletion. Inhibition of intracellular Ca^{2+} cycling and the influx of extracellular Ca^{2+} also blocks maximum ROS production and protects the cells. GSH depletion is not sufficient to cause the maximal mitochondrial ROS production, and there is an early requirement for protease activation, changes in gene expression, and a late requirement for Ca^{2+} mobilization (Tan *et al.*, 1998; Battaglia *et al.*, 2004). Neuroprotection from ischemia (*i.e.*, excess glutamate) is afforded by radical-scavenging flavonoids (Rivera *et al.*, 2004).

Kainic Acid

Kainic acid (KA) is an analog of the excitatory amino acid neurotransmitter glutamate. KA is known to depolarise both pre- and postsynaptic cells by interaction with the non-NMDA type of glutamate receptor. KA, like domoic acid, is an unnatural agonist at the so-called kainate receptor, producing excitotoxicity in brain (Olney *et al.*, 1979; Nadler *et al.*, 1980; Siao *et al.*, 2003). Upon administration of KA in rodents, KA produces acute status epilepticus and neuronal damage that is restricted to a discrete reproducible spatial pattern that includes lesions in the pyramidal CA1 and CA3 regions of the hippocampus (Sperk *et al.*, 1983). In the hippocampus, the cell death occurs with features of apoptosis such as DNA laddering (Filipkowski *et al.*, 1994; Pollard *et al.*, 1994) and with the morphological characteristics of necrosis (Fujikawa *et al.*, 2000).

Not to be ignored, is the high sensitivity of immature oligodendrocytes to kainate, an effect mediated by nitric oxide (NO) (*i.e.*, toxicity was prevented by inhibition of NO synthase) and through AMPA receptors (*i.e.*, toxicity was prevented by the AMPA antagonist DNQX) (Martinez-Palma *et al.*, 2003). The liability of astrocytes following hypoxia/ischemia is thought to be attributable to such an excitotoxic mechanism.

Domoic Acid

Domoic acid, a tricarboxylic amino acid analogue of glutamic acid that acts as an agonist at the kainic acid receptor, is found in the environment as an algae-derived contaminant of some seafood, particularly shellfish. In 1987, domoic acid was identified as the causative toxin in an episode of mussel poisoning that affected several hundred people in Canada. *Postmortem* evaluation revealed neuropathological damage in the deceased patients' brains, predominantly involving the hippocampus and amygdala (Gjedde and Evans, 1990; Perl *et al.*, 1990; Teitelbaum *et al.*, 1990). A down-regulated expression of the NMDAR1 receptor subunit and up-regulation of neuronal nitric oxide synthase mRNA were also reported at a time of active neurodegeneration in the rat hippocampus, supporting the involvement of both excitotoxic mechanisms and an inflammatory necrotic response in domoic acid toxicity (Ananth *et al.*, 2003). Human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein 120 (gp120) alone is associated with microglia activation and neuronal caspase-dependent apoptotic pathway (Acquas *et al.*, 2004). In the past decade evidence indicating a role for excitatory amino acids in association with neurological disorders has been accumulating (Chandrasekaran *et al.*, 2004). And more recently, domoic acid was found to exert it neurotoxixity at an early stage of ontogeny (*i.e.*, low dosage, 5 or 20 μg, daily in rats 8-14 days after birth) (Doucette *et al.*, 2004).

OTHER NEUROTOXINS AND RELATED CHEMICAL SPECIES

Veratridine

Veratridine, a Na^+ channel site 2 agonist, induces an increase in intracellular Na^+ concentration ($[Na^+]_i$), cellular depolarization, elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), glutamate release, swelling and death in neuronal cells (Ohta *et al.*, 1973; Ramnath *et al.*, 1992; Hubert *et al.*, 1994). All the changes induced by veratridine described above are observed in neurons during cerebral ischemia. Studies on the effects of veratridine-induced neuronal toxicity on sodium channel gene expression, in primary forebrain cultures enriched in neurons, shows a quantitative changes in the expression of various NaCh genes in neurons and suggest that the $Na_v1.1$ sodium channel gene may play a key role in

the neuronal injury/recovery process (Dave *et al.*, 2003a). Recent novel studies include the use of RS100642-198, a sodium channel blocker, as a neuroprotectant against hypoxia/hypoglycaemia (Dave *et al.*, 2001), and able to reverse the veratridine-induced down-regulation in the $Na_v1.1$ sodium channel gene (Dave *et al.*, 2003a).

3-Nitropropionic Acid (3-NP)

In aged rats, chronic administration of 3-NP causes selective striatal lesions (Brouillet *et al.*, 1998), and this effect has been used as a model for the neuropathology of Huntington's disease (HD) (Beal *et al.*, 1993). 3-NP is an irreversible inhibitor of the enzyme succinate dehydrogenase (SDH), which functions both in the tricarboxylic acid cycle and electron transport chain complex II-III (Alexi *et al.*, 1998; 2000; Brouillet *et al.*, 1999). 3-NP impairs energy metabolism by inhibiting SDH that leads to ATP depletion and the accumulation of lactate (Alexi *et al.*, 1998).

Mitochondrial dysfunction by 3-NP interferes with ATP synthesis and causes oxidative stress in neurons (Alexi *et al.*, 1998). Treatment of cultured rat hippocampal neurons with 3-NP resulted in two types of cell death with distinct morphological, pharmacological, and biochemical features: 1) acute excitotoxic necrosis and 2) delayed apoptosis (Pang and Geddes, 1997) - although 3-NP was not nearly as neurotoxic as complex I inhibitors (Xu *et al.*, 2003). In fact, 3-NP produced 'pre-conditioning', or protection of hippocampal neurons from subsequent hypoxia/ischemia (Sugino *et al.*, 1999).

Peroxynitrite Anion

Peroxynitrite-induced neurotoxicity is thought to be an important mechanism of neuronal injury in hypoxic-ischemic brain and spinal cord injury (Szabo, 1996) and a variety of neurodegenerative disorders, such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS) (Chabrier *et al.*, 1999; Heales *et al.*, 1999). Peroxynitrite, a product formed in a near diffusion-limited reaction of nitric oxide and superoxide (Beckman and Koppenol, 1996; Martinez-Palma *et al.*, 2003), is a strong oxidizing agent that causes DNA damage (Szabo and Ohshima, 1997), lipid peroxidation (Radi *et al.*, 1991), and protein nitration (Crow *et al.*, 1997; Ara *et al.*, 1998).

The mode of cell death induced by peroxynitrite can be necrosis, apoptosis, or mixed types of cell death, depending on peroxynitrite concentration, on the duration of peroxynitrite exposure, and on intracellular ATP levels (Bonfoco *et al.*, 1995; Leist *et al.*, 1997). Activation of poly(ADP-ribose) polymerase by damaged DNA is suggested to be a major cause of peroxynitrite-induced necrosis (Eliasson *et al.*, 1997; Szabo, 2003).

Peroxynitrite (0.25-0.75 mM) had virtually no effect on cell viability of astrocyte monolayers prepared from neonatal rat spinal cord, demonstrating the resistance of astrocytes to this oxidant. However, long processes - positive for glial fibrillary acidic protein (GFAP) - developed in a large number of astrocytes, indicative of a reactive astrocytic phenotype (Pehar *et al.*, 2002). Peroxynitrite has proven to be a useful chemical tool for studies relating to ALS (Barbeito *et al.*, 2004).

Tetrahydrocannabinol

Tetrahydrocannabinol (Δ^9-THC) in marijuana is well known as a drug associated with dependence or addiction. 2-Δ^9-and Δ^8-THC were toxic when added directly to SH-SY5Y neuroblastoma cells (Klegeris *et al.*, 2003). 11-OH-Δ^9-THC produced neurotoxicity, as assessed by evaluation of electroencephalograms recorded from rats (Colasanti, 1985). It appears that a magnesium deficiency, even a moderate one, may aggravate the neurotoxicity of THC at low doses and, reciprocally, that low doses of THC may reveal the potential neurotoxicity of a moderate magnesium deficiency (Bac *et al.*, 2003). Δ^9-tetrahydrocannabinol, the main active principle derivative of the marijuana plant, induces impairment in spatial memory and a decrease in acetylcholine release in the dorsal rat hippocampus (Inui *et al.*, 2004; Manzanares *et al.*, 2004). The role of endocannabinoids in neurodegenerative disorders was recently reviewed (van der Stelt *et al.*, 2003).

Soman

Organophosphorus compounds such as warfare neurotoxicants (sarin, soman, tabun, VX) are irreversible cholinesterase inhibitors. Soman (pinacolyl methylphosphono-fluoridate)., is among the most powerful of these and the most dangerous warfare neurotoxicant. Exposure to the organophosphorus nerve gas soman causes a progression of toxic signs including hypersecretion, respiratory distress, tremor, seizures/convulsions, coma, and death (Taylor, 2001). This spectrum of toxic effects is attributable to irreversible inhibition of acetylcholinesterase, the enzyme that hydrolyzes acetylcholine, resulting in excessive synaptic acetylcholine and consequent over-stimulation of

muscarinic and nicotinic receptors. Increased cholinergic activity in the brain induces the first phase of seizures (Lallement *et al.*, 1992; McDonough and Shih, 1997), whereas sustained seizures (status epilepticus) are probably associated with increased glutamatergic activity leading to excitotoxic damage predominantly in the hippocampus, amygdala, piriform, and entorhinal cortices (Carpentier *et al.*, 1991; McDonough and Shih, 1997). There is continued study of quaternary pyridinium aldoximes that can reactivate organophosphate-inhibited acetylcholinesterase (Kuca *et al.*, 2004).

Alterations in brain glutathione homeostasis are induced by the nerve gas soman (Klaidman, *et al.*, 2003). Hippocampal slice cultures were exposed daily during 1 week to a transient level of soman that produced no evidence of synaptic deterioration. However, after the subtoxic soman treatments the tissue became vulnerable to a brief episode of glutamate receptor overstimulation that normally resulted in little or no excitotoxic damage. These findings indicate that seemingly innocuous soman exposures leave the hippocampus sensitive to the types of insults implicated in traumatic brain injury and stroke (Munirathinam and Bahr, 2004).

Trimethyltin

Trimethyltin (TMT) is a prototypic hippocampal neurotoxin that produces loss of dentate granule cells and pyramidal neurons predominantly in the rat hippocampal CA3 region (Bouldin *et al.*, 1981; Chang and Dyer, 1983; Whittington *et al.*, 1988; Harry *et al.*, 2004). Behaviorally, TMT intoxication is characterized by seizure, self-biting, aggressive behavior, hyperactivity and impaired working memory (Ishida *et al.*, 1997).

Metyrapone, an inhibitor of corticosteroid synthesis, not only improved TMT-induced damage in the hippocampus, but also alleviated TMT-induced learning impairment as well as hyperactivity (Tsutsumi *et al.*, 2002). Thus, TMT-induced neurotoxicity may be associated with the altered function of hypothalamo-pituitary-adrenocortical axis, since the hippocampus contains the highest density of corticosteroid receptors in the central nervous system (McEwen *et al.*, 1968).

Recently TMT was shown to reduce levels of mRNA for the amyloid precursor protein (APP) containing 695 amino acids (APP695) in the regions of the hippocampus in which there was evidence of degeneration (eosinophilia and TUNEL-positive neuronal cells (Nilsberth *et al.*, 2002). In addition, TMT induced enhanced expression of pro-inflammatory cytokines such as IL-1α, IL-6, and TNF-α (McCann *et al.*, 1996; Bruccoleri *et al.*, 1998), increased cell cycle genes cyclin A2, cyclin B1 and cyclin D1 - the latter in regions in which there was evidence of necrosis, and microglia differentiation to a phagocytic phenotype (McPherson *et al.*, 2003). Because increased cycle gene expression was not associated with microglia proliferation (*i.e.*, BrdU incorporation and Ki-67 immunoreactivity), it is hypothesized that the cyclins may promote differentiation of microglia to the phagocytic phenotype (McPherson *et al.*, 2003).

The other interesting area of investigation resulting from a TMT study, was the report of increased neurogenesis in the hippocampus of mice after TMT-induced loss of dentate granule neurons - as indicated by increased BrdU uptake, Ki-67 immunocytochemistry, and increased levels of nestin and doublecortin (Harry *et al.*, 2004).

HEAVY METAL NEUROTOXINS

Iron

A pivotal role of iron in the pathogenesis of PD has been emphasized because of its ability to enhance the production of $HO^{\cdot}$ and to accelerate neuronal degeneration (Sofic *et al.* 1988; Dexter *et al.*, 1993; Shoham and Youdim, 2000; Berg *et al.*, 2002; Andersen, 2003; Gerlach *et al.*, 2003). Total iron level in the SN of PD patients is elevated compared to age matched controls (Sofic *et al.*, 1988; 1991). The mechanism of action of iron has been suggested to be dependent on the ability of free Fe^{2+} to catalyze the formation of $HO^{\cdot}$ in Fenton chemistry. It is plausible that extracellular free iron exists when iron-binding proteins are saturated under iron overload. The role of neuromelanin in SN neurons is unresolved - although neuromelanin sequesters iron and stores it as Fe^{3+} (a neuroprotective role) (Solano *et al.*, 2000; Wilczok *et al.*, 2000). Neuromelanin also thus serves as a sink for Fe^{2+}, perhaps releasing it under adverse conditions to exert deleterious effects (Gerlach *et al.*, 2003). Reductants such as ascorbic acid, flavins ($FMNH_2$ and $FADH_2$), rivboflavin, sulfide, thiols (L-cysteine and glutathione) and dopamine release iron from ferritin (Laulhere *et al.*, 1996; Double *et al.*, 1998; Cassanelli and Moulis, 2001). Thiols also release iron from monoferrictransferrin (Baldwin *et al.*, 1990). Recently, it was found that binding of the haloperidol metabolite 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]pyridinium ion (HPP^+), which chemically resembles MPP^+, to melanin had a major influence of HPP^+-induced neurotoxicity to primary cultures of rat embryonic mesencephalon (Kawashima *et al.*, 2004).

A new mechanism for iron neurotoxicity has been

reported, since iron toxicity is dependent on (i) Fe-dopamine complex formation, (ii) uptake through the monoaminergic transporter, and (iii) inhibition of DT-diaphorase by dicoumarol. This neurotoxicity is inhibited by nomifensine, reboxetine and norepinephrine (Paris *et al.*, 2005). Also, Youdim *et al.* (2004) have synthesized a family of bifunctional drugs that inhibit MAO and chelate iron, and thereby afford neuroprotection.

Copper

Copper neurotoxicity is observed in Wilson's disease, which is an autosomal recessive disease with a mutation in the ATP7B gene, resulting in functional impairment of the ATP7B protein. The impairment of ATP7B-mediated intracellular copper transport results in accumulation of hepatic copper due to both reduced biliary copper excretion and abrogation of ceruloplasmin synthesis. Wilson's disease may present with a variety of clinical conditions, the most common being liver disease and neuropsychiatric disturbances. Regarding neurological disturbances, Parkinsonian symptoms predominate, but pseudosclerotic, dystonic, and choreic symptoms can also be found, often associated with a change in personality (Loudianos and Gitlin, 2000; Riordan and Williams, 2001). As expected, these clinical features mirror the underlying pathological alterations, with prominent degeneration in the basal ganglia, extensive gliosis, and neuronal loss in association with a marked increase of the copper content in this region of the brain (Loudianos and Gitlin, 2000). Young copper-miners has been detected with parkinson syndrome (Caviedes and Segura-Aguilar, 2001). The mechanism of the neurotoxic action of copper in dopaminergic neurons seems to be dependent on (i) formation of Cu^{2+}-DA complex; (ii) Selective uptake of Cu^{2+}-DA complex via the DA transporter; (iii) oxidation of DA by Cu^{2+}, generating intracellular aminochrome; and (iv) one-electron-reduction of aminochrome to leukoaminochrome-*o*-semiquinone radical (Paris *et al.*, 2001).

Manganese

In young miners of manganese (Mn) ore in the United States, Chile, former Soviet Union, Cuba, Morroco, Japan, India, Taiwan and China, there is an abnormally high incidence of an atypical parkinsonian syndrome characterized by dystonia and infrequent tremor. Evidence from *in vitro* and *in vivo* experimental models demonstrates that Mn produces oxidative stress and free radical-induced damage of nigrostriatal pathways. Oxidative stress-induced apoptosis may be a mechanism of cell death in Mn-induced parkinsonism. Superoxide dismutase and catalase effectively prevent Mn-induced death of cultured fibroblasts, while vitamin E attenuates striatal DA loss (for review, see Pal *et al.*, 2001). Mn^{3+} *per se* is neurotoxic by virtue of its oxidizing DA to aminochrome (*o*-quinone), which is capable of promoting subsequent formation of the very potent neurotoxic leukoaminochrome-*o*-semiquinone radical, by one-electron reduction (Archibald and Tyree. 1987; Segura-Aguilar and Lind, 1989; Arriagada *et al.*, 2004; Diaz-Veliz *et al.*, 2004).

Lead

Lead (Pb^{2+}) has been known for centuries to be a neurotoxin, able to cross the blood-brain barrier more readily in children than in adults, and impair ontogenetic development of brain - adversely affecting cognitive ability and producing behavioral abnormalities. Lead induces blood-brain barrier dysfunction when administered even at low doses, producing "leaky" microvessels that are implicated in a variety of neuropathological conditions (Struzynska *et al.*, 1997). The mechanisms of lead neurotoxicity are complex and still not fully understood, but recent findings recognized that both Ca^{2+}-dependent proteins (Bressler *et al.*, 1999) and neurotransmitters receptors represent significant targets for Pb^{2+} (Ishihara *et al.*, 1995). In particular, acute and chronic exposure to lead would predominantly affect two specific protein complexes: protein kinase C and the *N*-methyl-D-aspartate subtype of glutamate receptor. These protein complexes are deeply involved in learning and cognitive functions and are also thought to interact significantly with each other to account for altered functions (for review, see Marchetti, 2003).

Mercury

Organomercurials with a short aliphatic chain are the most harmful compounds and they may cause irreversible damage to the nervous system (Sanfeliu *et al.*, 2003). Methylmercury (CH_3Hg^+) is the most studied. The high thiol reactivity of CH_3Hg^+, as well as all mercury compounds, has been suggested to be the basis of their harmful biological effects (Aschner and Clarkson, 1988). The main mechanisms involved are inhibition of protein synthesis, microtubule disruption, increase of intracellular Ca^{2+} with disturbance of neurotransmitter function, oxidative stress and triggering of excitotoxicity mechanisms (Cheung and Verity, 1985; Freitas *et al.*, 1996; Miura *et al.*, 1998; 1999; Castoldi *et al.*, 2000;

Gasso *et al.*, 2000; Heidemann *et al.*, 2001; Sanfeliu *et al.*, 2003). The effects are more damaging during CNS development, leading to alterations of the structure and functionality of the nervous system (Sanfeliu *et al.*, 2003). The major source of CH_3Hg^+ exposure is the consumption of fish and, therefore, its intake is practically unavoidable if fish is a dietary constitutent.

SUMMARY

There is an ever increasing number of neurotoxins and neurotoxic species, and an ever more insightful understanding of their mechanisms of action. Neurotoxins that alter monoaminergic neurons are particularly useful for studies relating to Parkinson's disease: MPTP/MPP^+, 6-OHDA, salsolinol, leukoaminochrome *o*-semiquinone radical, iron, copper, manganese, and paraquat. 3-NP is particularly useful for modelling the neuropathology of Huntington's disease. TMT provides a damaged neuropil that is a good step-off point to study neurogenesis in brain. Glutamate, kainate, and domoate are excitotoxins useful for studying a variety of conditions and processes (*i.e.*, hypoxia/ischemia; reperfusion injury). Peroxynitrite also is beneficial particularly in studying hypoxic-ischemic brain and spinal cord injury. Soman is an organophosphate used as nerve gas, and it provides the step-off point for discovery of aldoximes that can reactivate organophosphate-inhibited acetylcholinesterase. Other neurotoxins described in this review are additionally useful for delimiting the mechanisms invoked for neuronal necrosis and apoptosis. As old targets are better understood and as new mechanistic targets become defined, there is increased potential for development of drugs to interrupt irreversible neuronal cell death. The value of neurotoxins for uncovering mechanisms involved in neuronal cell death is expansive.

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