ELSEVIER

Brain Research Reviews 36 (2001) 1-22

BRAIN RESEARCH REVIEWS

www .elsevier .com / locate / bres

Review

Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment

Colin Davidson[3], Andrew J. Gow[c], Tong H. Lee[3], Everett H. Ellinwood[3,b] *

[a]Department of Psychiatry, Box 3870, Duke University Medical Center, Durham, NC 27710, USA
[b]Department of Pharmacology, Box 3870, Duke University Medical Center, Durham, NC 27710, USA
[c]Department of Medicine, Box 3870, Duke University Medical Center, Durham, NC 27710, USA

Accepted 27 March 2001

Abstract

Research into methamphetamine-induced neurotoxicity has experienced a resurgence in recent years. This is due to (1) greater understanding of the mechanisms underlying methamphetamine neurotoxicity, (2) its usefulness as a model for Parkinson's disease and (3) an increased abuse of the substance, especially in the American Mid-West and Japan. It is suggested that the commonly used experimental one-day methamphetamine dosing regimen better models the acute overdose pathologies seen in humans, whereas chronic models are needed to accurately model human long-term abuse. Further, we suggest that these two dosing regimens will result in quite different neurochemical, neuropathological and behavioral outcomes. The relative importance of the dopamine transporter and vesicular monoamine transporter knockout is discussed and insights into oxidative mechanisms are described from observations of nNOS knockout and SOD overexpression. This review not only describes the neuropathologies associated with methamphetamine in rodents, non-human primates and human abusers, but also focuses on the more recent literature associated with reactive oxygen and nitrogen species and their contribution to neuronal death via necrosis and/or apoptosis. The effect of methamphetamine on the mitochondrial membrane potential and electron transport chain and subsequent apoptotic cascades are also emphasized. Finally, we describe potential treatments for methamphetamine abusers with reference to the time after withdrawal. We suggest that potential treatments can be divided into three categories; (1) the prevention of neurotoxicity if recidivism occurs, (2) amelioration of apoptotic cascades that may occur even in the withdrawal period and (3) treatment of the atypical depression associated with withdrawal.

Theme: Neural basis of behavior

Topic: Drugs of abuse: amphetamine and other stimulants

Keywords: Dosing regimen; Reactive species; Mitochondria; Dopamine; Treatments; Hyperthermia

Contents

1. Introduction 2
2. Clinical data 4
   2.1. Abuse patterns 4
   2.2. Psychopathology of withdrawal 4
3. Neuropathology in humans and non-human primates 4
4. Dosing regimen models and loss of monoamine function 5
   4.1. Early preclinical background 5
   4.2. Animal models of chronic methamphetamine abuse 5

*Corresponding author. Tel.: +1-919-684-5225; fax: +1-919-681-8369.
E-mail address: ehwood@duke.edu (E.H. Ellinwood).

0165-0173/01/$- see front matter
PII: S0165-0173(01)00054-6

4.3. Acute toxic dosing (ATD) model ... 5
4.4. Serotonergic neurotoxicity ... 6
4.5. Neurodegeneration in other brain areas ... 6
5. Insights from transgenic and knockout mice ... 6
5.1. DAT and $vMAT_2$ knockouts have opposite effects ... 6
5.2. nNOS knockout is neuroprotective ... 7
5.3. SOD over-expression is neuroprotective ... 7
5.4. cFos knockout exacerbates methamphetamine toxicity ... 7
5.5. Summary of knockout and transgenic data ... 8
6. Mechanisms of methamphetamine neurotoxicity ... 8
6.1. Dopamine oxidation ... 8
6.2. Methamphetamine and excitotoxicity ... 8
6.3. Effect of methamphetamine on mitochondria ... 10
6.4. A putative model of methamphetamine-mediated injury ... 10
6.5. Summary of oxidative mechanisms ... 12
7. Methamphetamine and hyperthermia ... 12
7.1. Effect of methamphetamine on body temperature ... 12
7.2. Effect of temperature on indices of dopamine function and neurotoxicity ... 12
7.3. Hyperthermia and NMDA receptor antagonists ... 12
7.4. Hyperthermia, NMDA receptors and neurotoxicity: exceptions to the rule? ... 13
8. Analogy to Parkinson's and other neurodegenerative disease models and putative treatments ... 13
8.1. Similarity to Parkinson's disease ... 13
8.2. Antioxidants, DAT and SERT inhibitors ... 14
8.3. Dopamine agonists ... 14
8.4. Monoamine oxidase inhibitors ... 14
8.5. The dilemma of drugs that may have both toxic and potential protective effects: tetrahydrobiopterin ... 15
8.6. Potential harm by certain treatments: disulfiram ... 15
9. Summary ... 15
Acknowledgements ... 15
References ... 15

1. Introduction

Methamphetamine (MA; /V-methyl-O-phenyl isopropylamine) is a cationic lipophilic molecule with potent action on the sympathetic and central nervous systems. Repetitious high-dose abuse of amphetamines (e.g., d-amphetamine (AMPH) or MA binges) result in near steady-state plasma levels and can lead to a prolonged (6-12 months) withdrawal period. This raises the question of whether neurotoxicity, or at least some long-term functional changes have led to the extended withdrawal rather than the usual, more moderate, anergia and psychoasthenia associated with stimulant withdrawal. PET imaging and post-mortem studies in humans have shown decreases in indices of dopamine (DA) function, however, more detail of MA neurotoxicity has been gleaned from animal studies. Such studies, currently are using predominantly one-day acute toxic dose (ATD) MA, have shown loss of DA and serotonin (5-HT) terminals and related pathology. The early prevailing view was that these neurotoxic effects were the result of a direct chemical insult. MA enters the terminals/neuron via the DA or 5-HT transporter (DAT and SERT, respectively) and displaces both vesicular and intracellular DA/5-HT. These displaced amines are oxidized (by MAO and auto-oxidation) to reactive oxygen species (ROS; [44,186]), with further production of ROS via H_2O_2 and NO [20] resulting in necrotic cell death. However, over time other mechanisms have been added including glutamate- [131,228] and peroxynitrite- [14] mediated neurotoxicity. Thus both reactive oxygen and nitrogen species (RONS) may be involved. It has also been shown that MA, due to its lipophilicity, can diffuse through cell membranes including intracellular organelles, for example, mitochondria, where it disrupts the electrochemical gradient. It is thus possible that MA not only kills neurons by the direct production of free radicals but also by triggering a mitochondrial-dependent induction of apoptotic cascades [188]. It appears, therefore, that MA can kill neurons by multiple mechanisms over an extended time scale (Fig. 1). Therapeutic intervention should thus be directed at these mechanisms with due regard to the time after withdrawal.

MA neurotoxicity has been reviewed previously [9,19,110,155,175,186,187]. The current review mainly focuses on recent progress with specific regard to: (1) laboratory models that reflect the distinction between chronic binging versus ATD; (2) the different types and time course of neurodegenerative processes; (3) possible MA-induced mechanisms of neurotoxicity; (4) necrotic versus apoptotic mechanisms; (5) discussion of short and long-term tolerance versus neurotoxic structural changes; (6) potential for preventing later apoptotic cascades and

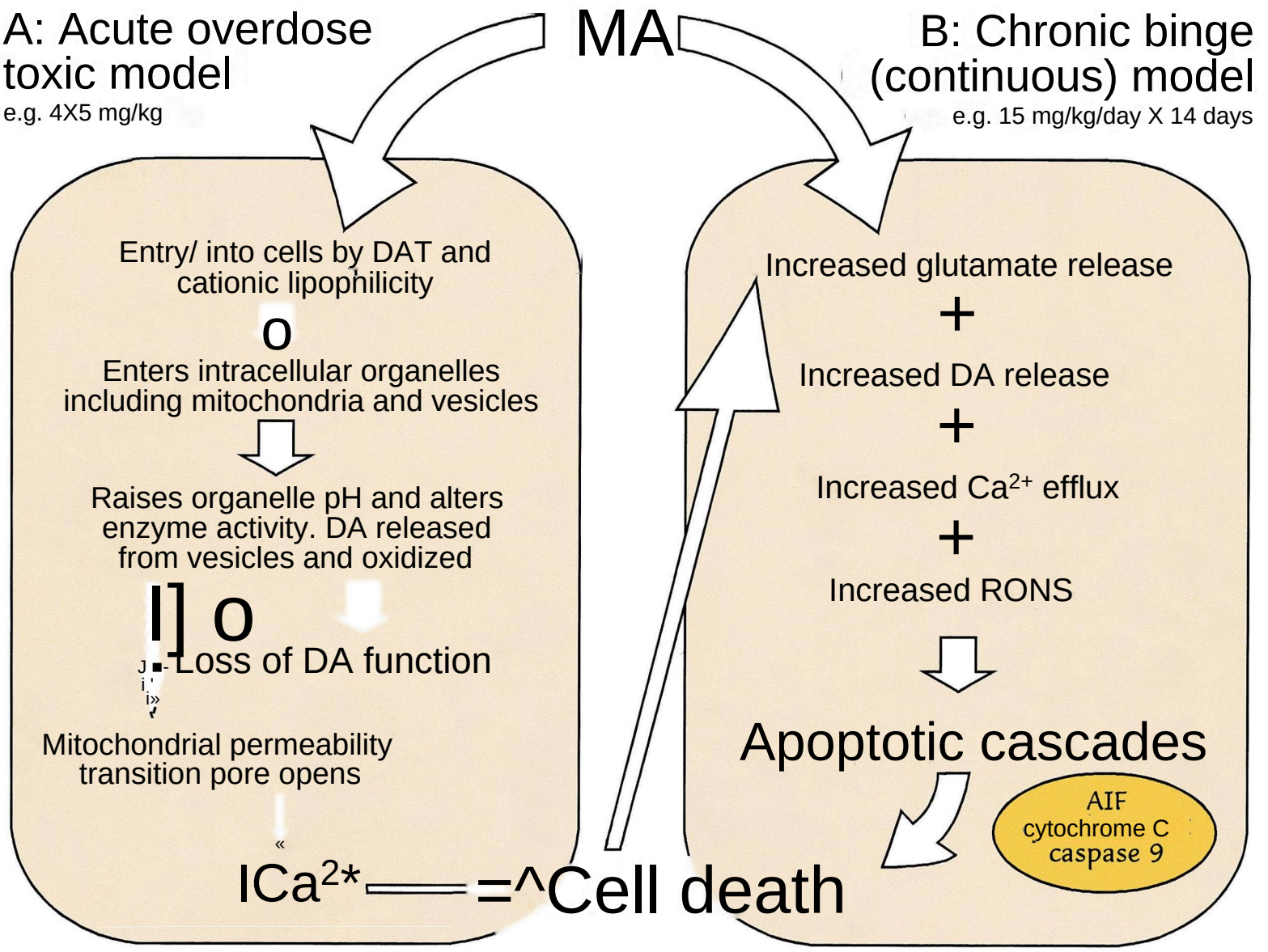

Fig. 1. Acute versus chronic methamphetamine models. A simplified cartoon of two models of MA dosing. These processes may actually take place in parallel or in series. The acute toxic model results in, essentially, loss of DA function whereas the chronic model results in apoptosis. However, both regimens can result in necrotic and/or apoptotic cell death. MA, methamphetamine; DAT, dopamine transporter; RONS, reactive oxygen and nitrogen species; AIF, apoptosis inducing factor.

facilitating remodeling and long-term recovery and (7) issues relating to the appropriate time after withdrawal for the initiation of potential treatments.

2. Clinical data

2.1. Abuse patterns

Stimulant binging is characterized by frequent (every 2 h) large doses over many days and compulsive repetitive MA abuse has been described many times. Previously, and even now in Japan and in the U.S. Mid-West, 'speed freaks' inject compulsively (8-10 times per day) at high doses (0.3-1.0 g) daily for three to 10 days [113,118]. The shortest $t_{1/2}$ of MA is 5-6 h ranging up to 34 h [6] dependent on urine pH. Yet compulsive MA abusers are administering it at short inter-dose durations (e.g., 2 h), thus near steady-state plasma levels are quickly reached with modest fluctuations. Massive tolerance to the lethal effects can develop since these doses are five to six times the LD_{50} in a naive user. Thus laboratory models that administer MA two or more times a day for a number of days or continuously may best reflect this clinical condition.

There are two common scenarios for MA overdose and death. Often, after an extended abstinence, an MA abuser will relapse and take a very high dose, which had previously been taken, when in a tolerant state. Having lost his tolerance (hyperthermia, hypertension, seizures) to MA during withdrawal, this high dose will be lethal. Similarly a new abuser will often take the same high dose of MA that an experienced (tolerant) associate is capable of taking, which will be lethal to the non-tolerant individual. Death is preceded by uncontrollable hyperthermia, seizures, hypoxic stress, and may be compounded by hypertensive crises and associated cardiovascular complications. This condition is reflected in the common laboratory model of administering ATD MA (e.g., 10 mg/kgX4 q. 2 h).

2.2. Psychopathology of withdrawal

The anergia including dysphoria and lack of mental energy associated with withdrawal from high-dose MA abuse is much more severe than that seen with cocaine and may wax and wane for months after withdrawal [57]. Psychosis is also common in MA abuse and a predisposition to paranoia can last for years, however, psychosis may not have a connection to neurotoxicity since cocaine can induce psychosis while having little, if any, neurotoxicity. Thus some long-term functional change, or neurotoxicity, may be superimposed on the usual stimulant withdrawal characterized by a 1-3 week period of anergia and psychoasthenia. The latter shorter-term symptoms are more frequently found in cocaine bingers and also in lower-dose MA abusers [101]. Currently there is not a clear understanding of the contribution of long-term tolerance versus neurotoxicity to the long-term withdrawal syndrome (or indeed whether the two phenomena are related) yet clear understanding of these issues are critical in developing potential treatments during withdrawal.

3. Neuropathology in humans and non-human primates

A recent post-mortem study [223] reported that chronic MA users of unknown abuse intensity had significantly decreased levels of DA, tyrosine hydroxylase (TH), and DAT (the last assessed by [^{3}H]WIN 35428 and [^{3}H]GBR 12935 binding and immunological staining for DAT) in the caudate and putamen. In contrast, the vesicular monoamine transporter type-2 ($vMAT_2$) and DOPA decarboxylase levels showed no changes between controls and chronic MA abusers. The authors comment that the loss of DA nerve terminals as a consequence of neurotoxicity would be expected to reduce all of the measured presynaptic DA markers, as has been shown to occur in idiopathic Parkinson's disease (PD [222,223,230]). However, McCann et al. [137] makes a case for neurotoxicity: In the first PET study to examine MA abusers it was shown that caudate and putamen DAT ([^{n}C]WIN-35428) binding was reduced even after 3 years of abstinence. The authors questioned whether the reduction in DAT binding reflected neuroadaptation (i.e. fewer DAT sites on an unchanged number of DA terminals; e.g., [223]) or neurotoxicity (i.e. fewer DA terminals). Although differences in drug use patterns (acute versus chronic) could account for differences between these two studies, the large body of evidence from non-human primates (vide infra) showing MA-induced neurotoxicity with similar doses of MA, supports the view that neurotoxicity accounted for reduced DAT binding. Lieberman et al. [129] have made a case for extended tolerance/neurotoxic effects that may explain the chronic 'bum out' condition in former speed freaks. Wilson et al. [223] have also suggested that decreased DA levels (-50% of control), even if not indicative of neurotoxicity, are consistent with motivational changes reported by MA abusers in the early and intermediate withdrawal period. More recently, Voikow and colleagues have found detoxified MA abusers to have reduced DAT binding in the caudate and putamen [213], reduced glucose metabolism in the thalamus, caudate and putamen but an increased metabolism in the parietal cortex [214].

In an early study Seiden et al. [185], examined the early (24 h after) and long-term (3-6 months after) effects of chronic (3-6 months) MA in rhesus monkeys. Losses in the NE and DA systems were found, the most striking loss was that of DA in the caudate which was 80% depleted with little recovery by 6 months. Furthermore, as shown previously [67] this dosing regimen induced behavioral

tolerance to MA. The 'permanent' nature of these monoamine losses was shown by Woolverton et al. [225], who found a similar dosing regimen to have reduced DA and 5-HT concentrations in the caudate 4 years after MA withdrawal. Thus early studies with non-human primates emphasized the importance of chronic MA regimens in relation to neurotoxicity. Common findings include loss of markers for DA and 5-HT function with a relative sparing of the NE system (see [186] for a review).

Recently, Melega et al. [140], using 6-[^{18}F]fluoro-L-DOPA PET, showed that 10 days of an escalating AMPH dose (4-18 mg/kg, i.m.) decreased DA synthesis capacity in Vervet monkeys 6 months after treatment. More recently the same group [141] have extended these studies and found a slow recovery (both neurochemical and behavioral) from the profound initial changes with almost complete recovery after 2 years. Villemagne et al. [211], reported in baboons a dose-dependent (0.5,1 and 2 mg/kg, i.m., X4) decrease in [^{u}C]WIN-35,428 binding by PET scanning, a finding confirmed by post-mortem decreases in [^{3}H]WIN-35428 and [^{3}H]DTBZ binding and decreased DA and DOPAC levels in both the caudate and putamen. This study also showed a decrease in 5-HT and its primary metabolite 5-HIAA in the caudate and putamen. Importantly, and in contrast to a loss of DAT sites (which should actually inhibit further MA action (tolerance) and neurotoxicity) the loss of vMAT$_2$ in the terminals allows for increased oxidation of cytosolic DA and increased levels of oxidative species with enhanced susceptibility to oxidative damage [171,205,71]. More recently Melega et al. [143] has shown glial derived neurotrophic factor (GDNF) to be neuroprotective against MA-induced loss in DAT sites in the vervet monkey.

In summary, the human and non-human primate studies show long-term losses in DA and 5-HT function after chronic MA dosing. Future studies may use the vMAT$_2$ ligand [^{n}C]dihydrotetrabenazine (DTBZ [111]), which, when compared to [18^{f}]F-DOPA and DAT ligands such as nomifensine and WIN-35,428, may be a more sensitive and selective indicator of neurotoxic changes and/or long-term tolerance by MA. Regardless, elucidation of the nature of chronically altered mechanisms will facilitate predicting which potentially therapeutic drugs will be most effective and the duration of treatment needed.

4. Dosing regimen models and loss of monoamine function

4.1. Early preclinical background

The early observations by Escalante and Ellinwood [63] that chronically treated AMPH cats had neuronal chromatolysis and by Seiden et al. [185] that rhesus monkeys administered chronic high doses of MA had a depletion of caudate DA for at least 6 months afterwards, led investigators to speculate that MA was neurotoxic. Conclusive evidence of MA neurotoxicity was found by Ricaurte et al. [173,174], who showed DA terminal destruction using silver staining; the gold-standard for demonstrating neuronal degeneration [73]. Evidence of DA neuronal loss in the substantia nigra (SN) or ventral tegmental area (VTA) was not as convincing. Unfortunately, human post-mortem studies that follow months and years of high-dose abuse cannot use silver staining because the method is useful only in the days immediately after injury. Thus, in order to document neural degeneration in progress (using silver staining) and other measures of altered DA mechanisms, early post-mortem animal studies are necessary.

4.2. Animal models of chronic methamphetamine abuse

In rats, MA half-life is much shorter (<1 h; Melega et al. [139]); than in humans (6-34 h [6]); consequently, more sustained dosing models are needed to reflect the longer half-life and near steady-state plasma levels (and increased potential for neurotoxicity) in humans. Following continuous MA or AMPH infusion via osmotic minipumps, Ricuarte et al. [174] and Ryan et al. [180] found silver staining evidence for caudate neurotoxicity only at doses above 16-20 mg/kg/day; no significant toxicity was observed at lower doses. Ellison et al. [61] found that 12 mg/kg/day of MA, when given continuously by a silicon pellet, induced neurotoxicity but the pellet is a concentration-dependent release mechanism, probably releasing higher initial doses. In general, the chronic dosing models tend to provide more evidence of structural (neuronal cell body) damage.

4.3. Acute toxic dosing (ATD) model

ATD of MA (e.g., 4X10 mg/kg q. 2 h, s.c.) in naive animals is currently the most frequently used model in rats and is associated with hyperthermia and occasional seizures and also high mortality. This regimen provides: (1) excellent relevance to the acute high intravenous and smoked MA which induces extremely high brain levels on first pass extraction; (2) a model of the potential effects of MA in non-tolerant users and; (3) greater experimental control over variables.

Most recent studies have used ATD of MA and measured indices of DA function including TH, vMAT$_2$, DAT, DA, DOPAC and homo vanillic acid (HVA), using immunohistochemistry, high-performance liquid chromatography (HPLC) and microdialysis. Most data shows a loss of DA function in the dorsal striatum but a relative sparing in the accumbens shell [161]. This sparing may be related to a different density of DAT sites [23], an hypothesis supported by the protective effects of DAT blockers and DAT knockout (KO) mice. In a recent paper [34] it was shown that ATD of MA caused a reduction in evoked striatal DA

efflux and a reduction in rate of re-uptake as measured by voltammetry 1 week and 1 month after MA. These functional losses were much reduced by 6 months and have disappeared by 1 year after MA. The authors note that 'the time course for recovery, 6 months to 1 year, is substantially longer than would be expected if down-regulation was entirely responsible' and suggest that degenerating axons and terminals are responsible for their findings. A summary of chronic versus ATD, including DA depletion and structural changes, is found in Table 1.

4.4. Serotonergic neurotoxicity

The first studies to examine MA-induced 5-HT neurotoxicity found MA-treated (25 and 100 mg/kg/day, s.c., X4 days) rats to have a large depletion of 5-HT, with associated loss of SERT, 3 weeks after treatment [172] and a reduction in striatal and hippocampal tryptophan hydroxylase activity 30 days after ATD MA [94]. Originally it was thought that the regional specificity seen with DA terminals is not evident in the 5-HT system, with losses found in many disparate brain regions [172]. However Brown and Molliver [24] have recently shown selective damage in the caudate and accumbens core while, as with the DA system, 5-HT terminals appear to be spared in the medial shell 14 days after MA. This selective toxicity may be related to SERT density [24] and/or midbrain origin (DRN or MRN [116]). ATD of MA has been shown to decrease striatal synaptosomal 5-HT uptake by 50% 1 h after treatment [68] whereas cocaine, methylphenidate and fenfluramine were without effect suggesting that, as in the DA system, it is the intracellular actions of MA that appear to mediate its toxic effects. Cass [35] found ATD of MA to reduce evoked efflux of 5-HT in the striatum at 1 week and 1 month but to be normalized 6 months after treatment showing that restoration of the 5-HT system is possible. The SERT blockers (citalopram, clomipramine and fluoxetine) have been shown to be neuroprotective [94,183] as have DAT inhibitors in MA-induced DA neurotoxicity.

Serotonin toxicity could be related to the production of endotoxins such as tryptamine-4,5-dione (T-4,5-D), the major in vitro product of the superoxide-mediated oxidation of 5-HT [226]. This compound has been shown to uncouple mitochondrial respiration by irreversible inhibition of complex I and IV perhaps by covalent attachment to sulfhydral residues [103]. The effect of MA on mitochondria is discussed below with respect to DA neurons. Thus MA-induced neurotoxicity of the 5-HT system has some similarities to that in the DA system.

4.5. Neurodegeneration in other brain areas

While this review, and the majority of the literature, focuses on changes in the DA system it should be noted that neurodegeneration may occur in other brain areas after MA or AMPH. For example, neurodegeneration has been found in the piriform and parietal cortex [21,184], thalamus and hippocampus [21,22,184], areas which receive only a sparse dopaminergic input, and in non-DA striatal elements [27]. Interestingly, a recent study in humans [213] shows lower glucose metabolism in the thalamus (—17%), caudate (—12%) and putamen (—6%) and an increase in the parietal cortex (+6%) in detoxified MA abusers

5. Insights from transgenic and knockout mice

5.1. DAT and $vMAT_2$ knockouts have opposite effects

Fumagalli et al. [70], using ATD of MA found that tissue DA content in wild-type (Wt) was 20% of controls with no loss in DAT KO mice. Levels of the metabolites fell dramatically in both KO and Wt suggesting that the lipophilic MA can enter the terminal regardless of DAT. Regardless it may be that a fully active DAT system is needed to produce DA neurotoxicity. There was a less marked decrease in 5-HT and its metabolites. Thus the

Table 1
Evidence of neurotoxicity due to acute or chronic toxic AMPH/MA dosing

Acute toxic dosing			Chronic toxic dosing		
Species	Effect on DA cell bodies and terminals	Evidence of recovery	Species	Effect on DA cell bodies and terminals	Evidence of recovery
Rat	TD[1-4], TSS[4]	~8 months[3,4]	Rat	rppl3- 19, rpQQ 13-15,17,19, OSS[17,19]	Little
Mouse	TD[5-8], ND[5], NSS[5]	?*	Cat	TD[2°],ND[2°],TandNSS[20]	None
Primate	TD[9 l2],ND[9]. TSS[11]	3-9 months[9,10,12]	Primate	TD[21–27], TSS[25,26], ND[21,24,25], NSS[25]	Modest[20,21], None 4 years[19]
			Human	rpj-j28,29	?

A representative summary of the effect of either acute toxic dosing or chronic dosing on dopamine (and other) cell bodies and terminals. N.B. This is a sample not an exhaustive list. T, DA terminal; D, depletion (e.g., DA, TH, DOPAC); N, DA neuron; SS, silver stain, i.e. loss of structure; OSS, other silver staining (non-DA). *the majority of these studies sacrifice the mice only a few days after MA.[1] [50],[2] [20],[3] [69]; [4] [34],[5] [196],[6] [70],[7] [90],[8] [100],[9] [185],[10] [141],[11] [211],[12] [143],[13] [59],[14] [173],[15] [174],[16] [215],[17] [180],[18] [178],[19] [60],[20] [63],[21] [185],[22] [159],[23] [177],[24] [166],[25] [225],[26] [140],[27] [141],[28] [223],[29] [137],

DAT may only partially contribute to 5-HT neurotoxicity. These data suggest, therefore, that MA-induced DA neurotoxicity is partially mediated by efflux of DA to the extracellular space via the DAT. An alternative model suggests that intraneuronal oxidation is the primary cause of DA terminal neurotoxicity [45]. This view is consistent with Cappon et al. [32] who showed that 20-day-old rats were refractory to MA and had fewer DAT sites and lower tissue DA content. Interestingly DAT KO showed no increase in temperature after ATD of MA whereas both heterozygotes and Wt showed a 2°C elevation [70].

To further examine the question of whether MA-induced DA neurotoxicity is mediated via extra- or intracellular DA, Fumagalli et al. [71], examined heterozygous $vMAT_2$ KO (homozygotes are not viable after ~1 week). It was again found that ATD of MA resulted in decreased DA and metabolite levels in the striatum of Wt, however, heterozygotes displayed greater toxicity. Interestingly it had previously been shown that synaptosomal uptake of DA was the same in both Wt and heterozygote mice [72] supporting the hypothesis that differences found in MA neurotoxicity in vMAT, heterozygotes are linked to the $vMAT_2$ not the DAT. Thus vesicular functional capacity is important in the defense against DA oxidation and related neurotoxicity.

5.2. nNOS knockout is neuroprotective

It has been shown that NMDA receptor activation allows Ca^{2+} into the cell, binding of Ca^{2+} with calmodulin activates nNOS which produces NO and hence peroxynitrite [12]. Furthermore, inhibition of nNOS by 7-nitroindazole (7-NI) prevents MA-induced DA toxicity [54,99]. Given these findings Itzhak et al. [100], examined the effect of MA on nNOS KO mice. After ATD of MA it was found that KO nNOS mice showed no loss in mazindol binding or decreases in DA, DOPAC and HVA, further, these mice did not exhibit an MA-induced hyperthermia. Interestingly, at baseline, nNOS KO mice had reduced levels of DA that could be related to the lack of MA neurotoxicity. Regardless, nNOS activation appears crucial to MA neurotoxicity.

5.3. SOD over-expression is neuroprotective

A role for ROS in MA-induced neurotoxicity has been proposed. For example, inhibition of SOD by diethyldithiocarbamate increases neurotoxicity [50]. Subsequently, Cadet et al., [29], using mice that overexpress SOD found chronic MA to induce no loss of DA or DOPAC in the striatum or cortex of SOD overexpressing Tg mice when compared to Wt. Similarly, Hirata et al. [90] found these transgenic (Tg) mice displayed a six-fold increase in SOD activity and showed only a small reduction in DAT binding after ATD of MA when compared to Wt. Because increased SOD is neuroprotective against MA it was hypothesized that the superoxide ion was more important than the H_2O_2 or hydroxyl radical in MA-induced neurotoxicity (see section on 'MA and oxidative stress').

Because MA-induced toxicity is attenuated in SOD-overexpressing Tg mice, Jayanthi et al. [102] examined whether MA had a differential effect on antioxidant enzymes in these mice. ATD of MA caused a decrease in SOD, catalase and glutathione peroxidase in both cortical and striatal regions in Wt but an increase in SOD and catalase in Tg mice; furthermore lipid peroxidation was increased in both cortices and striata in Wt but not in Tg mice. Interestingly ATD of MA still causes an elevation of striatal and cortical c-fos and zif268 in both groups of mice [92]. This effect could be by mediated by indirect activation of DA D, receptors [147] or glutamate receptors [219] although manipulations that cause oxidative stress in general also increase these immediate early genes (IEGs [46,84]). The elevations in c-fos and zif268 were, however, attenuated in SOD Tg mice. Nevertheless these data suggest that MA can activate IEGs in a superoxide-independent pathway.

5.4. cFos knockout exacerbates methamphetamine toxicity

Although MA has been shown to induce c-fos [92] it remains unclear whether the c-fos induction confers a neurotoxic or neuroprotective effect. It has also been shown that Tg mice that overexpress SOD showed a marked attenuation of IEG responses [92] and AP-1 binding activity [189,190]. Mice lacking c-fos [105,218] were given ATD of MA and killed 1 week after treatment. MA injections caused a marked decrease in [^{125}I]RTI-121 binding in striatum and this pathology was potentiated in c-fos KO mice [49]. There was also a concomitant loss of DAT and TH. Measurement of apoptotic DNA fragmentation (using TUNEL stain) 3 days after MA again showed potentiated MA-induced toxicity in c-fos KO mice both in striatum and non-DA neurons in the cortex. Conversely c-fos KO mice showed an attenuated increase in the number of astrocytes, which have been shown to synthesize and release neurotrophic factors [176], produced in response to MA as measured by glial fibrillary acidic protein (GFAP) immunoreactivity, c-fos can activate some antioxidant enzymes such as glutathione S-transferase [146,165] and stimulate the antioxidant response element in the human NADPH:quinone oxidoreductase gene [126]. c-fos can also increase levels of trophic factors such as nerve growth factor (NGF [88,191]). Thus c-fos induction by toxic doses of MA might serve as an oxidative stress response that could activate downstream molecular and cellular events that are neuroprotective and could be associated with increased tolerance.

5.5. Summary of knockout and transgenic data

An important caveat with regard to KO and Tg mice is that they are not just different from Wt with respect to loss of a particular protein; there are also numerous unknown compensatory developmental mechanisms working. In particular c-fos is involved in the regulation of numerous genes and, as such, c-fos KO mice are very different from Wt in many ways. Regardless, DAT KO mice were found to be refractory to MA which suggests that the DAT-mediated neurotoxic pathways are important, while the vMAT$_2$ KO data suggest that intracellular DA (oxidation) is more important in toxicity. However, nNOS KO are also refractory to MA, which highlights the importance of NMDA receptor activation in neurotoxic pathways. The SOD overexpressing Tg mice highlight oxidative mechanisms, specifically the superoxide and peroxynitrite radicals. Finally, the induction of IEGs by MA is probably the first stage in a number of neuroprotective mechanisms.

6. Mechanisms of methamphetamine neurotoxicity

As the previous section has shown there is an increasing body of evidence that MA-induced neurotoxicity is dependent upon the production of reactive species, irrespective of MA's mode of entry into the neuron. There are three basic mechanisms by which MA administration could result in the production of such species; (1) DA release and subsequent enzymatic oxidation, (2) DA auto-oxidation and (3) mitochondrial disruption. Aberrant release of DA can also induce oxidative stress by excitatory amino acid (EAA) excitotoxicity through increased glutamate release (Fig. 2).

6.1. Dopamine oxidation

As already mentioned DA and/or its metabolites can generate ROS. DA is metabolized by MAO to DOPAC and H_2O_2 [198]. In addition, DA can be non-enzymatically oxidized by molecular O_2 to form radical semi-ubiquinones and superoxide radicals [82]. Cheng [39] has demonstrated that anti-oxidants provide neuroprotection against DA-induced cell death in cell models. Treatment with antioxidants, ascorbic acid, or glutathione reduces the formation of protein-bound cysteinyl cathechols, a further indication that DA oxidation products may contribute to toxicity [85].

6.2. Methamphetamine and excitotoxicity

Cadet and Brannock [30] recently reviewed the evidence that oxidative stress is involved in MA-induced toxicity. In addition to the already mentioned DA oxidation and ROS production, MA administration can lead to increased extracellular glutamate concentration [153,154,199,228]. The consequent NMDA receptor activation will lead to increased production of reactive species [131], in particular through the production of arachidonic acid and NO via the coordinated action of nNOS. Glutamate receptor antagonists attenuate MA toxicity, inhibiting the fall in DA content and TH activity [194,195] and inhibiting gliosis [144]. These neuroprotective effects may be related to glutamate receptor antagonist-induced hypothermia [3,4,145], although MA has been shown to produce hyperthermia at low doses [89,124,148,162,170]. In contrast, diethyldithiocarbamate inhibition of SOD increased neurotoxicity [50]. There continues to be compelling evidence that superoxide radicals are involved in neurotoxic effects of MA.

It is entirely probable that MA-induced toxicity occurs through the combined action of nitrosative and oxidative stresses. Perhaps most convincingly both nNOS KO and SOD overexpression are neuroprotective in response to MA (vide supra), implying that RONS are involved. In this context it is worth noting that selenium is a potent inhibitor of MA-induced neurotoxicity [96,109]. Selenium is most effective as a scavenger of two electron oxidants, such as peroxynitrite, and is not particularly reactive towards single electron oxidants, such as NO and superoxide. Therefore, it would appear that MA-induced toxicity is a result of the combination of these reactive species. Importantly, however, reactive species generation is not merely toxic in this process.

Wink and Mitchell [224] have described the biology of NO as divided into two categories: direct and indirect effects. The direct effects, in which NO interacts with biological targets, are generally rapid and require very low concentrations of NO, i.e. the physiological effects of NO. The indirect effects derive from the reaction between NO and other oxidants to form RONS.

Thus at low flux these reactive molecules can have a number of physiologically significant roles including transcription factor regulation and cellular signaling [227]. At higher rates of production these species are susceptible to a variety of cellular defense mechanisms such as SOD and glutathione. However, the interaction of NO and ROS generation can result in the formation of higher oxides of nitrogen, which are potent pathological mediators. Most prevalent among such oxides is the product of NO and O_2^-, peroxynitrite. NO and O^ are both free radicals, however, they are only mild one electron oxidants. Due to their radical nature they recombine rapidly, indeed production of peroxynitrite is close to diffusion limited (the reaction is three-fold faster than the reaction of O_2^- with SOD [13]). Peroxynitrite is a potent two-electron oxidant as well as being capable of nitrating biomolecules. The balance between oxidation and nitration of target molecules is dependent upon the presence of CO_2. Peroxynitrite will readily combine with CO_2 to form a nitryl carbonate, which is capable of nitration but not oxidation [78]. Thus the production of peroxynitrite can result in a number of

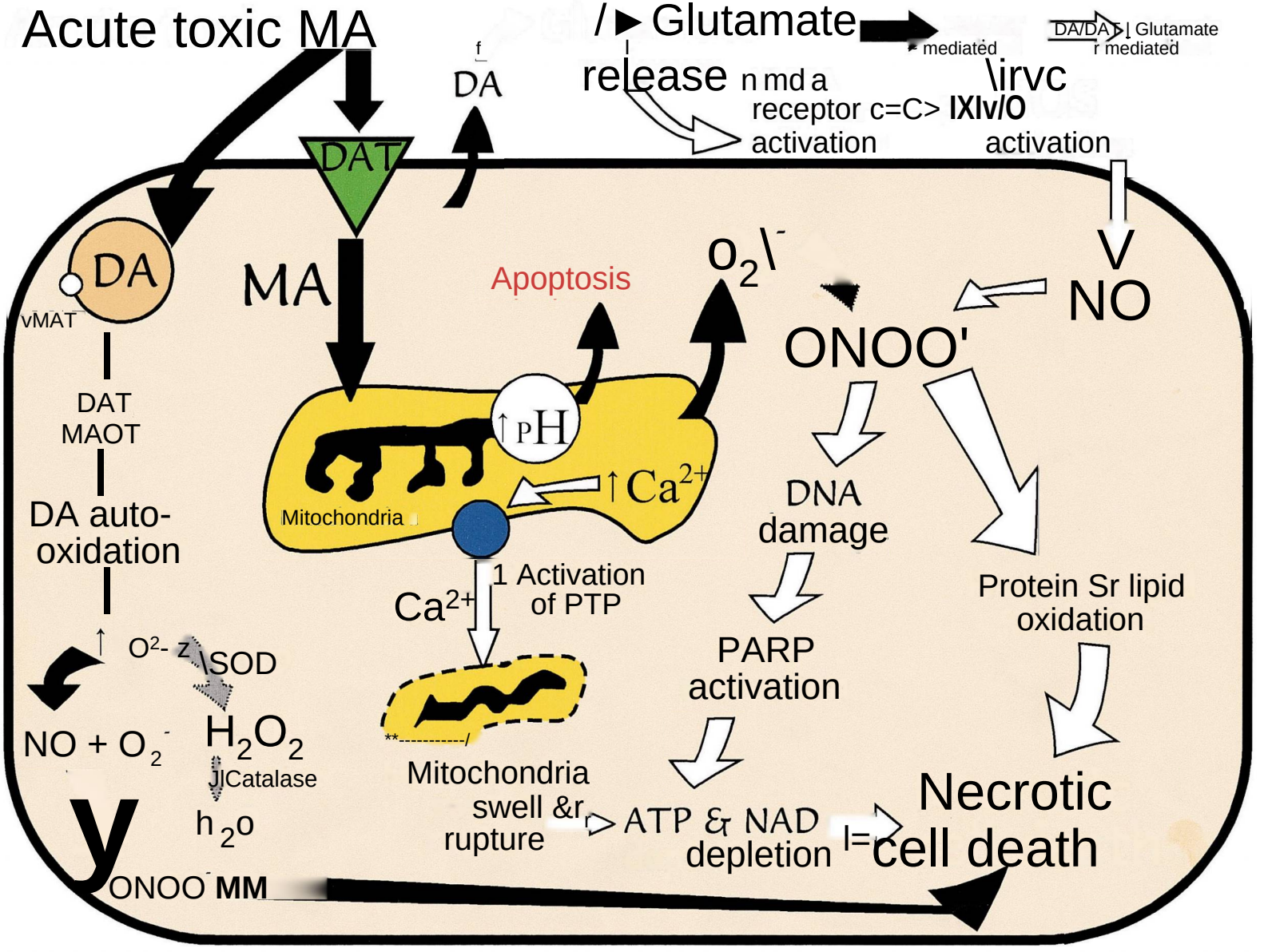

Fig. 2. Neurotoxic pathways of methamphetamine. MA enters the dopaminergic matrix and DA vesicles release DA which is oxidized by MAO and by auto-oxidation giving rise to superoxide (O_2^-). This reacts with nitric oxide (NO) to form peroxynitrite ($ONOO^-$) a highly reactive molecule which can cause necrotic cell death. There is considerable calcium release both by NMDA receptors and alterations in the mitochondrial permeability transition pore (PTP) which also results in cell death. Thus cell death can occur by both DA- and glutamate-mediated pathways. DA, dopamine; DAT, dopamine transporter; MA, methamphetamine; MAO, monoamine oxidase; PTP, permeability transition pore; PARP, poly (ADP-ribose) polymerase; ATP, adenosine triphosphate; NAD, nicotine adenine dinucleotide; NOS, nitric oxide synthase; NMDA, A-methyl-D-aspartate.

reactions including DNA strand breaks, nucleic acid modification, lipid oxidation, protein oxidation and nitration [47,108,114], which, in general, lead to necrotic cell death [79,81]. These reactions have been previously reviewed [80].

When considering the role of reactive species in MA-induced injury it is worth considering the role of tetrahydrobiopterin (BH_4). Within the SN BH_4 plays a critical role as a cofactor to two major enzymes: TH and NOS. Low levels lead to an inactivity of TH, however, within NOS there is some indication that a lack of BH_4 leads not to inactivity but to an alteration in product [136,192]. NOS is capable of generating both NO and ROS, such as superoxide, and the balance between these products is critically dependent upon the supply of substrate, L-arginine, and the presence of BH_4. When the intracellular concentration of BH_4 is low, TH activity will be inhibited, leading to an increase in the concentration of reducing equivalents. This increase, combined with low BH_4 levels, will result in NOS leaking electrons to molecular oxygen and increasing the flux of superoxide ions as well as NO, that is, a cytotoxic state. These proposals are supported by the observation that increased BH_4 levels are neuroprotective to DA neurons [115]. This issue is discussed further in a later section on tetrahydrobiopterin.

6.3. Effect of methamphetamine on mitochondria

Mitochondria have been implicated in both the necrotic and apoptotic cell death pathways with respect to neurodegenerative diseases [37]. Necrosis and apoptosis can occur: (1) either as distinct conditions alone, (2) in combination and (3) as sequential events. The necrotic pathway is usually induced by more severe toxic insults that result in ATP reserves being reduced beyond a critical level. For example, excitotoxins induce a prolonged mitochondrial membrane potential depolarization. Often when the insult is sufficient there is a depletion of energy reserves resulting in necrosis. When glutamate-induced excitotoxicity occurs the mitochondria accumulate Ca^{2+} [203]. There is a greater NOS production of NO following the increase in Ca^{2+} after stimulation of NMDA receptors versus stimulation of non-NMDA glutamate receptors [163].

MA administration can result in disruption of mitochondria via both direct and indirect mechanisms (Fig. 3). MA is a cationic lipophilic molecule that can diffuse into the mitochondria and be retained there. However, the accumulation of positively charged molecules in the cristae of the mitochondria will ultimately result in dissipation of the electrochemical gradient established by the electron transport chain (ETC). The gradient is essential to maintain ATP synthase (an acid pH enzyme) and also to sustain the integrity of the mitochondrial membrane [38]. Both of these functions are essential for cell survival and a failure in either result in the initiation of apoptotic processes [125]. The mitochondria possess calcium ATPase, which pumps Ca^{2+} into the inner mitochondrial space for storage purposes. The release of these stores, through the permeability transition pore (PTP) will result in activation of the cell death cysteine proteases, caspases, in particular caspase-3, which is normally associated in its inactive state with the mitochondrial envelope [150]. Another proapoptotic factor, which can be released from dysfunctional mitochondria, is cytochrome-c which is an essential cofactor of complex IV within the ETC, and is released from the complex upon damage. Once these factors have been released and the apoptotic cascades have been initiated they are essentially irreversible (Fig. 3).

As previously mentioned there are a number of ways in which MA can result in the production of reactive species. The mitochondrion is itself a source of ROS through leakage from the ETC and is particularly susceptible to such molecules. The main sites for oxidative attack are the PTP and the four complexes of the ETC. The PTP is readily oxidized which results in pore opening and Ca^{2+} release. This may be one of the main sites of action of DA semiquinones as the PTP is structurally very close to the MAO enzyme. The ETC, while susceptible to oxidative attack, is much more sensitive to nitrogen oxides [87]. Cytochrome c oxidase of complex IV is a heme protein and as such rapidly combines with NO to produce a ferrous nitrosyl complex. Although this combination is reversible, the Iron NO bond is very strong and thus low levels of NO can effectively inhibit complex IV function [42]. Indeed, such inhibition has been proposed as a mechanism for NO control of oxygen consumption [120]. Complexes I—HI are insensitive to NO, however, they are irreversibly modified by peroxynitrite both through oxidation and nitration [15]. Inhibition in this manner is likely to be catastrophic and result in mitochondrial explosion and cellular necrosis. It is worth remembering that DA neurons have a very high-energy demand and are thus particularly sensitive to mitochondrial damage. Indeed, they are extremely sensitive to the mitochondrial poison, rotenone [152],

6.4. A putative model of methamphetamine-mediated injury

There are thus a wide variety of mechanisms whereby MA administration can result in neuronal injury. However, examination of these mechanisms leads one to a time-dependent or sequential architectural model of the injury pattern. Initial insult with MA will result in a necrotic injury, most likely mediated by peroxynitrite, in those areas where MA accumulates, i.e. in those cells with the most abundant capacity (DAT) to take up MA. As a result of this necrotic cell death a number of species will be released into the surrounding interstitial space, including DA, glutamate, Ca^{2+}, NO, and ROS. This will then induce a more controlled sequential apoptotic cascade in the surrounding cells, and resistive adaptation in those cells

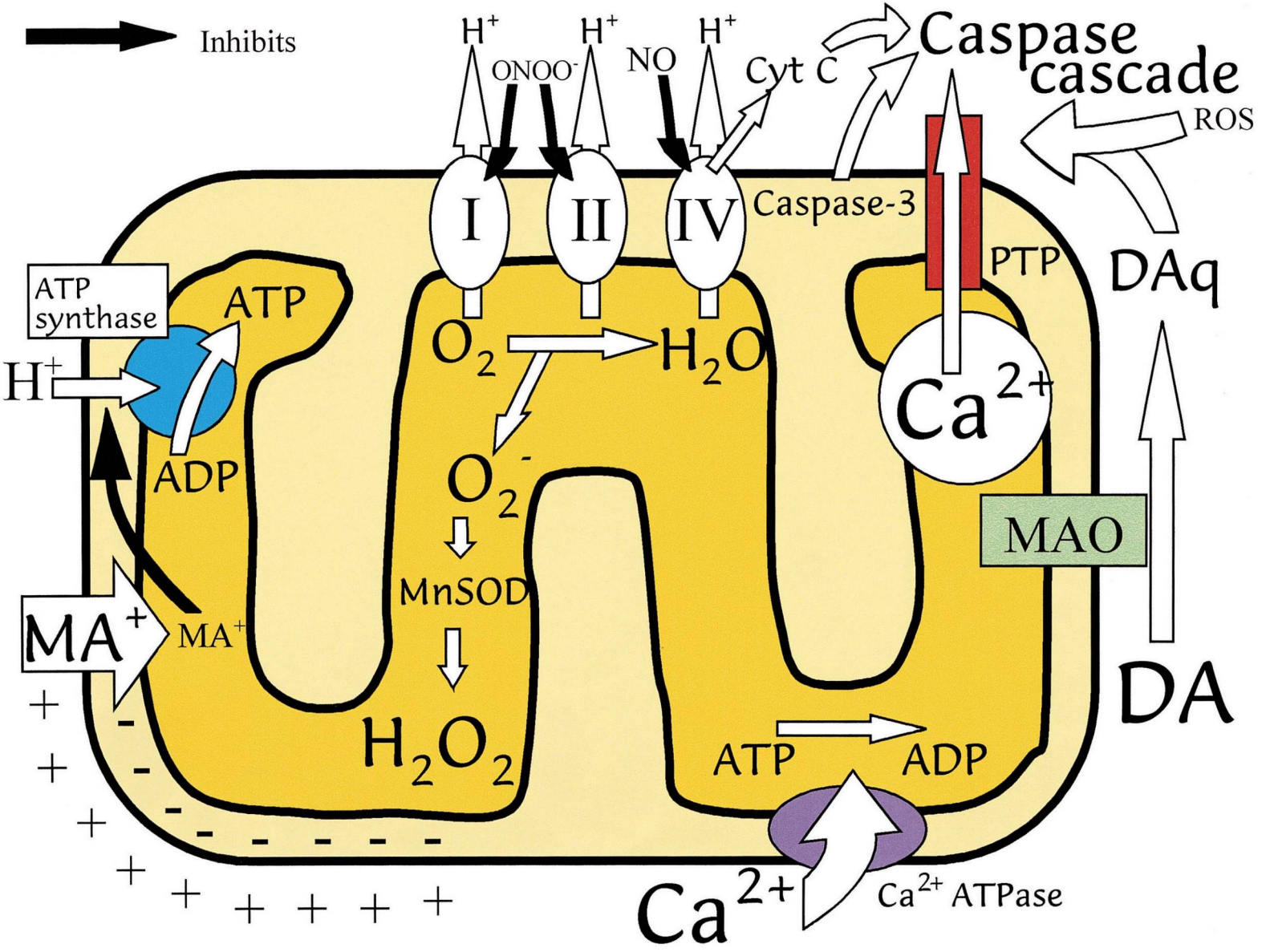

Fig. 3. Methamphetamine effects on mitochondria. MA enters mitochondria raising the pH of the inner membrane matrix; thus reducing the activity of the acid enzyme ATP-synthase. The capacity to maintain the mitochondrial membrane potential is thus reduced. Similarly (Fig. 2) MA inactivation of the vesicle proton (H^+) pump releases DA and increases formation of DA-quinones which open the permeability transition pore (PTP). Glutamate release by MA activates NMDA receptors, which increase production of nitric oxide (NO) which inhibits complex IV activating the caspase cascade. The formation of peroxynitrite ($ONOO^-$) from NO and superoxide ($O_2^{\cdot-}$) inhibits complex I and II. PTP, permeability transition pore; MAO, monoamine oxidase; MA, methamphetamine; DAq, dopamine-O-quinone; ROS, reactive oxygen species; Cyt C, cytochrome c.

that survive (most likely glial cells). Following the apoptotic phase there will be a period of regrowth where those surviving cells will attempt to repair the injured process; a reactive gliosis. In this way it may be that MA-induced injury can be modeled after stroke models of brain injury, where an initial necrotic site is surrounded by an apoptotic penumbra and the growth of existing cells into the damaged region [56].

6.5. Summary of oxidative mechanisms

MA enters the neuron, most likely in a predominantly DAT-dependent manner and increases flux of RONS (derived from nNOS). This increased flux may result from either the direct effect of MA or through released DA. Furthermore, NMDA receptor activation can produce ROS. The combined stresses of both oxidative and nitrosative stress result in necrotic, delayed, and apoptotic neuronal cell death. One likely molecular mediator of this injury process is peroxynitrite formed from the diffusion-limited reaction of NO with superoxide. The production of peroxynitrite can result in a wide range of pathological modifications of proteins, sugars, and lipids and has been implicated in neurological diseases as wide ranging as stroke and ALS.

By increasing the flux of reactive species, MA inhibits the mitochondrial electron transport chain resulting in massive release of Ca^{2+} through the PTP and the induction of apoptosis via the cytochrome c, caspase cascade. These cascades are most likely directly induced by MA incorporation into mitochondria and disruption of the electron gradient. It is possible that different cascades/pathologies arise from different MA dosing regimens. The initial necrotic injury from MA results in a release of neurotransmitters and reactive species into the milieu, which will result in disruption of the control of Ca^{2+} and oxidative stress in the surrounding area via a variety of processes. These processes may result in a region of apoptotic cell death occurring during the intermediate phase and further long-term effects such as cellular reorganization.

7. Methamphetamine and hyperthermia

7.1. Effect of methamphetamine on body temperature

It has been known for some time that amphetamine-induced hyperthermia contributes to lethality in man, however, hypertensive cerebrovascular hemorrhage and cardiovascular collapse may also contribute to deaths [106,229]. In rats temperatures may reach >40°C after each injection (e.g., [27,28,112,122,181]) where hyperthermia-induced death can occur. Chronic MA (20 mg/kg/dayX7 days) by osmotic minipumps is also hyperthermic for the first 2 to 3 days, and can also result in death (Davidson et al., unpublished observations). Indeed most researchers now attempt to control their experimental animal's temperature by means of ice-baths, cold rooms etc. in order to (1) reduce hyperthermic deaths and (2) rule out hyperthermia as a contributing factor to neurochemical and other changes. It has been shown that enhanced temperatures can increase oxidative stress in other systems [130,158,193] and, in addition to neurodegeneration from cerebrovascular damage, may be a mechanism whereby hyperthermia mediates neurodegeneration.

7.2. Effect of temperature on indices of dopamine function and neurotoxicity

Bowyer and colleagues were the first to specifically examine the effects of temperature on MA-induced neuroadaptations/toxicity and their interrelationships [16-18]. For example, is has been reported that while 4X10 mg/kg MA at 4°C evokes greater extracellular DA efflux than 4X5 mg/kg at 23°C, it produces neither hyperthermia nor loss of caudate DA content 3 days after MA. Conversely, the rats treated with the lower MA dose at room temperature showed a 35% loss in caudate DA content [17]. Furthermore, MA-induced hyperthermia is associated with striatal terminal degeneration (as shown by silver staining) whereas hyperthermia alone does not produce degeneration [18]. There is considerable evidence to suggest that the degree of changes in the DA system, or the degree of neurodegeneration, are correlated to the degree of hyperthermia. For example a correlation between core body temperature and loss of DA uptake [181] and between MA-induced decreases in striatal DA concentration and maximum body temperature [18] have been shown. Interestingly, the temperature in the caudate itself has been measured via a thermistor in a microdialysis probe and has been shown to parallel core body temperature after MA [41]. These findings suggest that extreme MA hyperthermia is associated with neurodegeneration but mild MA hyperthermia may result in loss of DA without neurodegeneration.

7.3. Hyperthermia and NMDA receptor antagonists

Antagonists of the NMDA receptor have been shown to be neuroprotective against MA in the DA system [149,169,194,195,197] and may be related to attenuation of increased DA efflux [156,221] although this is not always shown [10,66]. Glycine receptor antagonists are, however, ineffective [123]. Thus an inhibition of NMDA-induced increases in extracellular DA concentrations and NOS activation (see Fig. 2) may represent one neuroprotective mechanism. Indeed hyperthermia has been shown to increase calcium entry into the cell [54,201,202] thus inhibition of calcium entry (through the NMDA receptor) may be important. The NMDA receptor antagonist MK-801 (dizocilpine) may also have direct hypothermic effects, for example, MK-801 was shown to reduce hypoxic damage by lowering body temperature [25,43]. In fact,

many drugs which were originally thought to block various mechanisms associated with the action of MA have been shown to merely induce hypothermia [2,4,18,65]. Interestingly, the NMDA antagonist ketamine is found to be hypothermic, not when given alone, but when given with MDMA [132]. MK-801 also protects against MA-induced 5-HT functional loss [64,75,104,157,169] again consistent with NMDA-mediated calcium and/or temperature regulation mechanisms of neuroprotection.

7.4. Hyperthermia, NMDA receptors and neurotoxicity: exceptions to the rule?

Hyperthermia is certainly involved in MA-induced neurotoxicity and there are a number of mechanisms whereby these effects can be mediated (e.g., cerebrovascular damage, increased oxidative stress, increased calcium entry). In stark contrast to most rodent studies, however, Melega et al. [142] found that MK-801 and the resultant hypothermia did not reduce MA-induced 'neurotoxicity' (decreased WIN35428 binding) in the vervet monkey. It should be remembered therefore, that findings in one species (e.g., rat) may not correlate well with what is found in others (e.g., mouse, monkey) and may be dependent upon differences in MA pharmacokinetics [40]. However it would appear that glutamate-mediated actions and hyperthermia are not necessary for neuroadaptations to take place, at least in the vervet monkey. Conversely others have found no neurotoxicity in the post-natal day 20 rat after 4X10 mg/kg MA even though hyperthermia was evident [32]. More recently it has been shown that intrastriatal injection of AMPH can produce hydroxyl radicals without hyperthermia, and MK-801 can inhibit production of these free radicals [217]. The amphetamines can, therefore, cause NMDA-mediated oxidative damage without hyperthermia.

8. Analogy to Parkinson's and other neurodegenerative disease models and putative treatments

8.1. Similarity to Parkinson's disease

MA toxicity like that of MPTP is frequently cited (e.g., [196]) as a potential model of Parkinson's disease (PD). Conversely, it may be possible to gain insight into MA pathology from PD models. Once the first sign of PD has developed, retardation of the progression of the disease should be a major goal of treatment research. The same issue in a different form applies to MA toxicity. Should MA bingers be prophylactically treated during the early withdrawal and afterwards in order to prevent further pathology? The question of the mechanism responsible for the disease progression falls into two camps: (1) DA neuron areas have marginalized numbers of neurons that fail with the most severely affected areas being first, and the rest following in a more extended sequence [138] or (2) once an insult to one area of DA neurons has occurred, a secondary phenomenon, such as increased production of NO in glial cells continues to cause damage or apoptosis, not only to the original cells, but adjacent areas. A similar extended secondary damage is found in models of middle cerebral artery occlusion in which there are subsequent penumbral changes surrounding the infarct area [56]. We will primarily review the hypotheses based on the latter mechanisms.

If glial cells are involved in the progression over time after a neuronal insult, then an in vivo or ex vivo model rather than a cell line is essential. That is, the matrix support system around the DA neurons needs to be considered in treatment models. As one ages, or with toxic insult, the number of DA neurons decreases with a concomitant increase of astrocytes which contain higher levels of MAO-B. Thus one hypothesis is that the increased MAO-B relative to the DA neurons provides for an increased production of oxidative radicals.

It follows that drugs such as deprenyl, an MAOI as well as a ROS scavenger [74] may prevent the secondary cascades in MA toxicity. Other drugs that are utilized in the treatment of PD are direct DA agonists such as pramipexole, which also has antioxidant properties [36]. PD post-mortem histology reveals SN loss of DA neurons associated with a massive gliosis and the presence of active microglial cells [140] following DA neuron injury insults, such as with MPTP. The exaggerated SN gliosis [119], which is reported to be secondary to NO produced by glial cells, takes place in the neurons of mice in a time-dependent progression of events [128]. These authors found that iNOS was involved and that iNOS KO mice reduced the degeneration of the DA neurons following MPTP by 50%. Thus Liberatore et al. [128], demonstrated that the increased production of NO was a delayed response to MPTP, aggravating the original insult over time. The mechanism for MPTP neurotoxic activity is well known; it is taken up by glial cells where it is transformed by MAO-B to an active metabolite MPP^+ which is taken up by the DA neurons and inhibits complex I of the mitochondrial ETC [121]. Thus a DAT inhibitor and/or MAOI could be useful in the original insult stage of PD or MA neurotoxicity. In the original study of addicts who mistakenly took MPTP, there was a progressive PD syndrome, evidenced by sequential PET studies [212]. At autopsy, these patients also had numerous active microglial cells in the SN [121]. The mechanism by which NO induces neurotoxicity is under intense research effort. Indeed, elevated concentrations of nitrotyrosine are reported in the SN at autopsy in PD [77]. An additional potential mechanism involves NO release of iron from the intracellular buffer ferritin and the induction of oxidative damage via the Fenton reaction and its increase in ROS [1,93]. Interestingly, DA fibers and DA content in the

striatum are not spared from the toxic effects of MPTP in iNOS KO mice, which differs from that observed in nNOS KO mice [167]. Thus a model that examines ROS-induced toxicity over time needs to be used to examine the mechanisms involved and their prevention by drug treatments that inhibit NO production, as well as drugs that protect DA neurons by other means, such as reduction of MAO and by oxidant radical scavenging. This is especially true if one considers that considerable MA toxicity probably does not come from acute overdose but by repeated multi-day binges.

As a caveat, it should be noted that chronic MA abusers rarely show an increased incidence of PD, but may do as they age, at least the ones that survive their abuse. It should be noted that PD symptoms are only expressed when -90% of DA neurons are lost, thus MA could destroy many DA neurons with no PD symptomatology. Recent studies in detoxified MA abusers have, however, shown evidence for long-term neurotoxicity (reduced N-acetylaspartate, a neuronal marker) in the basal ganglia [62] and reduced metabolism [213] and DAT binding [214] in the caudate and putamen which is similar to that found in atypical PD [8]. Furthermore these patients have been shown to have motor and memory deficits [213]. To our knowledge there has been no long-term follow-up of the heavy MA abusers of the 1960s and 1970s, this group represents a population in which we would most likely be able to see PD develop if indeed MA contributes to this illness.

8.2. Antioxidants, DAT and SERT inhibitors

De Vito and Wagner [50,51] originally reported that ascorbate and vitamin E reduced MA neurotoxicity; thus along with the even more potent selenium [97,109] provide simple antioxidant treatments. The therapeutic use of uptake blockers for DA and 5-HT have been discussed above and multiple monoamine transport inhibitors are readily available (see Table 2).

8.3. Dopamine agonists

The loss of nigrostriatal DA neurons induced by ATD of MA is substantially blocked by pramipexole a DA $D_{2/3}$ agonist and antioxidant (1 mg/kg, p.o., 1 h after the last MA dose, plus daily thereafter [83]). The fact that the effects were observed as early as 5 days after MA exposure suggests that this may be due to a direct effect of MA at the level of SN neurons as opposed to a retrograde terminal degeneration. Casserino et al. [36] reported that pramipexole reduced the levels of ROS produced by MPP^+ when both were incubated with SH-SY5Y cells as well as when perfused into the striatum. Pramipexole also exhibited a concentration-dependent inhibition of opening of the mitochondrial PTP induced by Ca^{2+} and phosphate, or MPP^+ [36]. Sawada et al. [182] reported that preincubation with D_2-type DA agonists bromocriptine and quinpirole provides neuroprotection against glutamate-induced neurotoxicity in cultured rat mesencephalic neurons. However, when bromocriptine or quinpirole are only co-administered with MA they did not provide neuroprotection. The protective effects were dependent upon the duration of the preincubation and were blocked by D_2 antagonists and a protein-synthesis inhibitor. In addition, preincubation with D_2 agonists provided neuroprotection against toxicity induced by Ca^{2+} overload and exposure to superoxide anions [182]. Thus autoreceptor reduction of DA synthesis and release may substantially reduce MA neurotoxicity.

8.4. Monoamine oxidase inhibitors

Deprenyl (selegeline), an irreversible inhibitor of MAO-B is a frequently used adjunct therapy for PD. It is thought that the desmethyldeprenyl metabolites are also associated with an anti-apoptotic action in tissue culture and in animal models and is stereo-specific to the L-form [160,206]. In a kainic acid-induced toxic model, deprenyl increased hippocampal neuronal survival and is thought to have antioxidant properties. An added indication for looking at

Table 2
Putative pharmacotherapies for acute toxic dose methamphetamine

Treatment type	Example and reference
Antioxidant	Ascorbic acid',Vitamin E[1], nicotinamide[2'3], melatonin[4"6], selenium[7"9]
DAT inhibitor	Amfonelic acid[10'11], GB R12909[12], indatraline[12]
MAOI	Deprenyl* (selegiline)[13] although see [14,15]
DA agonists	Pramipexole[16]
NMDA antagonists	MK-801 (dizocalpine)[17-20] although see [21] **
Adenosine agonists	Caffeine[22], cyclopentyladenosine[22], CGS21680[23]
Opioid agonists	DADLE (8-opioid)[24-27], U69593 (K-opioid)[28]
SERT inhibitors	Fluoxetine[29], citalopram[30]***, clomipramine[30]
nNOS inhibitors	7-Nitroindazole (7-NI)[31,32]

Putative pharmacotherapies for acute toxic dose methamphetamine. *Metabolized to (—)MA and (—)AMPH. **This study done in vervet monkey. ***Also inhibits cytochrome P450 and thus MA metabolism.[1] [50],[2] [200],[3] [95],[4] [91],[5] [100],[6] [5]; [7] [96]; [8] [109]; ' [97]; [10] [183]; [11] [168]; [12] [179]; [13] [220]; [14] [216]; [15] [105]; [16] [83]; [17] [194]; [18] [104]; [19] [221]; [20] [169]; [21] [142]; [22] [46]; [23] [76]; [24] [208]; [25] [86]; [26] [209]; [27] [204]; [28] [55],[29] [94]; [30] [183]; [31] [53];
[32] [31]. DAT, dopamine transporter; MAOI, monoamine oxidase inhibitor; SERT, serotonin transporter; nNOS, neuronal nitric oxide synthase; DADLE, [D-Ala(2) ,o-Leu(5)]enkephalin.

deprenyl is that following 7 days of deprenyl treatment the magnitude of the subjective euphoria produced by cocaine infusions in humans was reduced by 40% [11]. It should be noted that all of the above putative treatments may not only work at the neuronal cell body level but may also provide protection at neuronal terminal sites

8.5. The dilemma of drugs that may have both toxic and potential protective effects: tetrahydrobiopterin

BH_4 presents the dilemma found not too infrequently with attempts to treat MA abusers for the withdrawal anergia and apathy but which may result in increased toxicity if they begin to abuse MA. Thus 6R-L-erythro-5,6,7,8 tetrahydrobiopterin (6R-BH_4) (which crosses the blood-brain barrier [98]) can augment TH in 6-OHDA-lesioned brains and could be useful for the withdrawal apathy; yet the synthesis-limited release of DA by MA would be augmented. Thus BH_4 presents a potential treatment dilemma which is also reflected in other potential treatments and underlines the need for interactive toxicology studies with MA before clinical testing. Liang and Kaufman [127], found that perfusion of rat striatal slices with L-arginine, which increases NO synthesis, induced a concentration-dependent increase of DA. This effect can be inhibited by SOD, whereas adding BH_4 induces a massive increase in DA release. The author suggests that the increase in DA release by BH_4 is dependent on its cofactor activity with NOS (nitric oxide synthase) and TH. Thus BH_4 is an active player in normal NOS and TH augmentation of DA release. Since BH_4 facilitates NOS, one might expect that its activation would promote neurotoxicity. However Kotsonis et al. [117], found that BH_4 reacted chemically with O_2 and enzyme-bound BH_4 was consumed under O_2-generating conditions in the absence of substrate [151]. DA neurons (which have high levels of BH_4) in culture are more resistant to the toxicity of both glutathione depletion and the treatment with peroxides than non-DA neurons regardless of their glutathione peroxidase status. Inhibition of BH_4 synthesis increased susceptibility of DA neurons to the toxicity of glutathione depletion, whereas increasing BH_4 levels completely protected non-DA neurons against toxicity. All these data are consistent with BH_4 serving to control NOS activity, in terms of product, i.e. reducing the aberrant production of ROS, and improving TH function. It is also possible that BH_4 itself serves to operate as an antioxidant. What is clear is that changes in the intracellular concentrations of BH_4 may contribute to some of the pathology found in the nigrostriatal system upon MA administration [207].

8.6. Potential harm by certain treatments: disulfiram

Currently many avenues to treatment of stimulant abuse are being explored to reduce craving and withdrawal symptoms. Carroll et al. [33] and Petrakis et al. [164] in double blind trials have documented that disulfiram, as a treatment for alcohol abuse, decreases cocaine abuse and is currently being considered as a treatment of combined cocaine and alcohol abusers. Disulfiram at low concentrations inhibits striatal synaptosomal uptake of DA as well as MPP^+, the toxic metabolite of MPTP [52], and there are other potential protective actions from ROS [48,134,135]. Despite these positive effects there are many reports indicating that disulfiram potentiates DA neurotoxicity. Originally it was demonstrated that disulfiram markedly potentiated the effects of MA leading to dystonia and potentiated seizure effects [58] and exacerbated MA depletion of DA [51]. More recent studies have demonstrated: (1) competitive inhibition at the peripheral benzodiazepine receptor, a component of PTP [107]; (2) striatal glutamate uptake inhibition and a decrease in Na^+K^+ ATPase [133]; (3) decreased DA uptake and increased release from vesicles [210]; (4) glutathione oxidation, DNA fragmentation and necrosis [26] and (5) inhibition of SOD [51]. Thus despite the evidence of protective effects, the majority of evidence is that disulfiram would aggravate neurotoxicity.

9. Summary

We suggest that acute toxic models of MA best represent acute overdose whereas chronic models represent the binging seen in many MA abusers. Following MA (especially chronic) treatment/abuse both short and long-term serial and parallel processes occur which result in apoptosis (Fig. 1). Further, we suggest that the MA-induced increase in extracellular glutamate promotes pathological NO synthesis with subsequent production of RONS which are the primary cause of neurotoxicity. Potential treatments could be directed at any stage in these pathways dependent upon length of abstinence. Finally it is interesting to note that MA neurotoxicity represents a good model of general EAA neurotoxicity and thus could be used to study PD, stroke, seizures and ALS.

Acknowledgements

We gratefully acknowledge funding by NIDA (DA-10327; DA-12768; DA-06519; U19 DA-109396) and the help of Dr Cindy Lazarus in preparation of this manuscript.

References

[1] P. Aisen, M. Wessling-Resnick, EA. Leibold, Iron metabolism, Curr. Opin. Chem. Biol. 3 (1999) 200-206.

[2] D.S. Albers, P.K. Sonasalla, Methamphetamine-induced hyperthermia and dopaminergic neurotoxicity in mice: pharmacological profile of protective and nonprotective agents, J. Pharmacol. Exp. Ther. 275 (1995) 1104-1114.

[3] S.F. Ali, G.D. Newport, R.R. Holson, W. Slikker, J.F. Bowyer, Low environmental temperatures or pharmacologic agents that produce

hypothermia decrease methamphetamine neurotoxicity in mice, Brain Res. 658 (1994) 33-38.

[4] S.F. Ali, G.D. Newport, W. Slikker, Methamphetamine-induced dopaminergic toxicity in mice. Role of environmental temperature and pharmacological agent, Ann. N.Y. Acad. Sci. 801 (1996) 187—198.

[5] S.F. Ali, J.L. Martin, M.D. Black, Y. Itzhak, Neuroprotective role of melatonin in methamphetamine- and l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine-induced dopaminergic neurotoxicity, Ann. N.Y. Acad. Sci. 890 (1999) 119.

[6] E. Anggard, L.E. Jonsson, A.L. Hogmark, L.M. Gunne, Amphetamine metabolism in amphetamine psychosis, Clin. Pharmacol. Ther. 14 (1973) 870-880.

[8] A. Antonini, K. Kazumata, A. Feigin, F. Mandel, V. Dhawan, C. Margouleff, D. Eidelberg, Differential diagnosis of parkinsonism with [18F] fluorodeoxyglucose and PET, Mov. Disord. 13 (1998) 268-274.

[9] K.J. Axt, L.A. Mamounas, M.E. Molliver, Structural features amphetamine neurotoxicity in the brain, in: A.K. Cho, D.S. Segal (Eds.), Amphetamine and Its Analogs: Psychopharmacology, Toxicology and Abuse, Academic, San Diego, 1994, pp. 315-367.

[10] H.A. Baldwin, M.I. Colado, T.K. Murray, R.J. De Souza, A.R. Green, Striatal dopamine release in vivo following neurotoxic doses of methamphetamine and effect of the neuroprotective drugs, chlormethiazole and dizocilpine, Br. J. Pharmacol. 108 (1993) 590-596.

[11] G. Bartzokis, L.L. Altshuler, T. Greider, J. Curran, B. Keen, W.J. Dixon, Reliability of medial temporal lobe volume measurements using reformatted 3D images, Psychiatry Res. 82 (1998) 11-24.

[12] J.S. Beckman, T.W. Beckman, J. Chen, P.A. Marshall, B.A. Freeman, Apparent hydroxyl radical production by peroxy nitrite: implications for endothelial injury from nitric oxide and superoxide, Proc. Natl. Acad. Sci. USA 87 (1990) 1620-1624.

[13] J.S. Beckman, W.H. Koppenol, Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly, Am. J. Physiol. 271 (1996) C1424-C1437.

[14] J.P. Bolanos, A. Almeida, V. Stewart, S. Peuchen, J.B. Clark, SJ. Heales, Nitric oxide-mediated mitochondrial damage in the brain: mechanisms and implications for neurodegenerative diseases, J. Neurochem. 68 (1997) 2227-2240.

[15] A. Boveris, L.E. Costa, JJ. Poderoso, M.C. Carreras, E. Cadenas, Regulation of mitochondrial respiration by oxygen and nitric oxide, Ann. N.Y. Acad. Sci. 899 (2000) 121-135.

[16] J.F. Bowyer, A.W. Tank, G.D. Newport, W. Slikker, S.F. Ali, R.R. Holson, The influence of environmental temperature on the transient effects of methamphetamine on dopamine levels and dopamine release in rat striatum, J. Pharmacol. Exp. Ther. 260 (1992) 817—824.

[17] J.F. Bowyer, B. Gough, W. Slikker, G.W. Lipe, G.D. Newport, R.R. Holson, Effects of a cold environment or age on methamphetamine-induced dopamine release in the caudate putamen of female rats, Pharmacol. Biochem. Behav. 44 (1993) 87-98.

[18] J.F. Bowyer, D.L. Davies, L. Schmued, H.W. Broening, G.D. Newport, W. Slikker, R.R. Holson, Further studies if the role of hyperthermia in methamphetamine neurotoxicity, J. Pharmacol. Exp. Ther. 268 (1994) 1571-1580.

[19] J.F. Bowyer, R.R. Holson, Methamphetamine and amphetamine neurotoxicity, in: L.W. Chang, R.S. Dyer (Eds.), Handbook of Neurotoxicity, Marcel Dekker, New York, 1995, pp. 845-870.

[20] J.F. Bowyer, P. Clausing, B. Glough, W. Slikker Jr., R.R. Holson, Nitric oxide regulation of methamphetamine-induced dopamine release in caudate/putamen, Brain Res. 699 (1995) 62-70.

[21] J.F. Bowyer, S.L. Peterson, R.L. Rowntree, J. Tor-Agbidye, GJ. Wang, Neuronal degeneration in rat forebrain resulting from d-amphetamine induced convulsions is dependent upon severity and age, Brain Res. 809 (1998) 77-90.

[22] J.F. Bowyer, Neuronal degeneration in the limbic system of weanling rats exposed to saline, hyperthermia or d-amphetamine, Brain Res. 885 (2000) 166-171.

[23] H.W. Broening, C. Pu, CV. Vorhees, Methamphetamine selectively damages dopaminergic innervation to the nucleus accumbens core while sparing the shell, Synapse 27 (1997) 153-160.

[24] P. Brown, M.E. Molliver, Dual serotonin (5-HT) projections to the nucleus accumbens core and shell: Relation of the 5-HT transporter to the amphetamine-induced neurotoxicity, The J Neurosci 20 (2000) 1952-1963.

[25] A.M. Buchan, Do NMDA antagonists prevent neuronal injury? No, Arch. Neurol. 49 (1992) 420-421.

[26] M.J. Burkitt, H.S. Bishop, L. Milne, S.Y. Tsang, GJ. Provan, C.S. Nobel, S. Orrenius, A.F. Slater, Dithiocarbamate toxicity toward thymocytes involves their copper-catalyzed conversion to thiuram disulfides, which oxidize glutathione in a redox cycle without the release of reactive oxygen species, Arch. Biochem. Biophys. 353 (1998) 73-84.

[27] K.B. Burrows, C.K. Meshul, High-dose methamphetamine treatment alters presynaptic gaba and glutamate immunoreactivity, Neurosci. 90 (1999) 833-850.

[28] K.B. Burrows, W.L. Nixdorf, B.K. Yamamoto, Central administration of methamphetamine synergizes with metabolic inhibition to deplete striatal monoamines, J. Pharmacol. Exp. Ther. 292 (2000) 853-860.

[29] J.L. Cadet, P. Sheng, S. Ali, R. Rothman, E. Carlson, C. Epstein, Attenuation of methamphetamine-induced neurotoxicity in copper/zinc superoxide dismutase transgenic mice, J Neurochem. 62 (1994) 380-383.

[30] J.L. Cadet, C. Brannock, Free radicals and the pathobiology of brain dopamine systems, Neurochem. Int. 32 (1998) 117-131.

[31] B.T. Callahan, G.A. Ricaurte, Effect of 7-Nitroindazole on body temperature and methamphetamine-induced dopamine toxicity, NeuroReport 9 (1998) 2691-2695.

[32] G.D. Cappon, L.L. Morford, C.V. Vorhees, Ontogeny of methamphetamine-induced neurotoxicity and associated hyperthermic response, Dev. Brain Res. 103 (1997) 155-162.

[33] K.M. Carroll, C. Nich, S.A. Ball, E. McCance, BJ. Rounsavile, Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram, Addiction 93 (1998) 713-727.

[34] W.A. Cass, M.W. Manning, Recovery of presynaptic dopaminergic functioning in rats treated with neurotoxic doses of methamphetamine, J. Neurosci. 19 (1999) 7653-7660.

[35] W.A. Cass, Attenuation and recovery of evoked overflow of striatal serotonin in rats treated with neurotoxic dose of methamphetamine, J. Neurochem. 74 (2000) 1079-1085.

[36] D.S. Cassarino, C.P. Fall, T.S. Smith, J.P. Bennett Jr., Pramipexole reduces reactive oxygen species production in vivo and in vitro and inhibits the mitochondrial permeability transition produced by the Parkinsonian neurotoxin methylpyridinium ion, J. Neurochem. 71 (1998) 295-301.

[37] D.S. Cassarino, J.P. Bennett Jr., An evaluation of the role of mitochondria in neurodegenerative diseases: mitochondrial mutations and oxidative pathology, protective nuclear responses, and cell death in neurodegeneration, Brain Res. 29 (1999) 1-25.

[38] B. Chance, G.R. Williams, The respiratory chain and oxidative phosphorylation, Adv. Enzymol 17 (1956) 65.

[39] N. Cheng, T. Maeda, T. Kume, S. Kaneko, H. Kochiyama, A. Akaike, Y. Goshima, Y. Misu, Differential neurotoxicity induced by l-DOPA and dopamine in cultured striatal neurons, Brain Res. 743 (1996) 278-283.

[40] A.K. Cho, W.P. Melega, R. Kuczenski, D.S. Segal, Relevance of pharmacokinetic parameters in animal models of methamphetamine abuse, Synapse 39 (2001) 161-166.

[41] P. Clausing, J.F. Bowyer, Time course of brain temperature and caudate/putamen microdialysate levels of amphetamine and dopamine in rats after multiple doses of D-amphetamine, Ann. N.Y. Acad. Sci. 890 (1999) 495-504.

[42] M.W. Cleeter, J.M. Cooper, V.M. Darley-Usmar, S. Moncada, A.H. Schapira, Reversible inhibition of cytochrome c oxidase, the terminal enzyme of the mitochondrial respiratory chain, by nitric oxide, FEBS Lett. 345 (1994) 50-54.

[43] D. Corbett, S. Evans, C. Thomas, D. Wang, R.A. Jones, MK-801 reduces cerebral ischemia injury by inducing hypothermia, Brain Res. 514 (1990) 300-304.

[44] J.F. Cubells, S. Rayport, G. Rajendran, D. Sulzer, Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress, J. Neurosci. 14 (1994) 2260.

[45] R. Datta, N. Taneja,V.P. Sukhatme, S.A. Qureshi, R. Weichselbaum, D.W. Kufe, Reactive oxygen intermediates target CC(A/T)6GG sequences to mediate activation of the early growth response 1 transcription factor gene by ionizing radiation, Proc. Natl. Acad. Sci. USA 90 (1993) 2419-2422.

[46] K.T. Delle Donne, P.K. Sonsalla, Protection against methamphetamine-induced neurotoxicity to neostriatal dopaminergic neurons by adenosine receptor activation, J Pharmacol. Exp. Ther. 271 (1994) 1320-1326.

[47] A.T. Demiryurek, I. Cakici, I. Kanzik, Peroxy nitrite: a putative cytotoxin, Pharmacol. Toxicol. 82 (1998) 113-117.

[48] S.N. Deneke, P.H. Harford, K.Y. Lee, C.F. Deneke, S.E. Wright, S.G. Jenkinson, Induction of cyctine transport and other stress proteins by disulfiram: effects on glutathione levels in cultured cells, Am. J. Respir. Cell Mol. Biol. 17 (1997) 227-234.

[49] X. Deng, B. Ladenheim, L.I. Tsao, J.L. Cadet, Null mutation of c-fos causes exacerbation of methamphetamine-induced neurotoxicity, J. Neurosci. 19 (1999) 10107-10115.

[50] M.J. De Vito, G.C. Wagner, Methamphetamine-induced neuronal damage: a possible role for free radicals, Neuropharmacology 28 (1989) 1145-1150.

[51] M.J. De Vito, G.C. Wagner, Functional consequences following methamphetamine-induced neuronal damage, Psychopharmacology 97 (1989) 432-435.

[52] D. Di Monte, I. Irwin, A. Kupsch, S. Cooper, L.E. DeLanney, J.W. Langston, Diethyldithiocarbanate and disulfiram inhibit MPP^+ and dopamine uptake by striatal synaptosomes, Eur. J. Pharmacol. 166 (1989) 23-29.

[53] D.A. Di Monte, J.E. Royland, M.W. Jakowec, J.W. Langston, Role of nitric oxide in methamphetamine neurotoxicity: protection by 7-nitroindazole, an inhibitor of neuronal nitric oxide synthase, J. Neurochem. 67 (1996) 2443-2450.

[54] I.A.S. Drummond, D. Livingstone, R.A. Steinhardt, Heat shock protein synthesis and cytoskeletal rearrangements occur independently of intracellular free calcium increases Drosophila cells and tissues, Radiat. Res. 113 (1988) 402-413.

[55] E. El Daly,V. Chefer, S. Sandill, T.S. Shippenberg, Modulation of the neurotoxic effects of methamphetamine by the selective kappa-opioid receptor agonist U69593, J. Neurochem. 74 (2000) 1553—1562.

[56] M.J.L. Eliasson, Z. Huang, R.J. Ferrante, M. Sasamata, M.E. Molliver, S.H. Snyder, M.A. Moskowitz, Neuronal nitric oxide synthase activation and peroxynitrite formation in ischaemic stroke liked to neural damage, J. Neurosci. 19 (1999) 5910-5918.

[57] E.H. Ellinwood, G. King, T.H. Lee, Chronic amphetamine use and abuse, in: S.J. Watson (Ed.), Psychopharmacology: The Fourth Generation of Progress CD-ROM, American College Neuropsychopharmacology, Lippincott, Williams and Wilkins, Philadelphia, PA, 1998, http://www.acnp.org/citations/GN401000166.

[58] E.H. Ellinwood Jr., A. Sudilovsky, R. Grabowy, Olfactory forebrain seizures induced by methamphetamine and disulfiram, Biol. Psychiatry 7 (1973) 89-99.

[59] G. Ellison, M.S. Eison, H.S. Huberman, F. Daniel, Long-term changes in dopaminergic innervation of caudate nucleus after continuous amphetamine administration, Science 201 (1978) 276-278.

[60] G. Ellison, Continuous amphetamine and cocaine have similar neurotoxic effects in lateral habenular nucleus and fasciculus retroflexus, Brain Res. 598 (1992) 353-356.

[61] G. Ellison, S. Irwin, A. Keys, K. Noguchi, G. Sulur, The neurotoxic effects of continuous cocaine and amphetamine in Habenula: implications for the substrates of psychosis, NIDA Res. Monogr. 163 (1996) 117-145.

[62] T. Ernst, L. Chang, M. Leonido-Yee, O. Speck, Evidence for long-term neurotoxicity associated with methamphetamine abuse, Neurology 54 (2000) 1344-1349.

[63] D. Escalante, E.H. Ellinwood Jr., Central nervous system cytopathological changes in cats with chronic methedrine intoxication, Brain Res. 21 (1970) 151-155.

[64] G.M. Farfel, G.L. Vosmer, L.S. Seiden, The V-methyl-D-aspartate antagonist MK-801 protects against serotonin depletions induced by methamphetamine, 3,4-methylenedioxymethamphetamine and p-chloroamphetamine, Brain Res. 595 (1992) 121-127.

[65] G.M. Farfel, L.S. Seiden, Role of hyperthermia in the mechanism of protection against toxicity. II. Experiments with methamphetamine, p-chloro amphetamine, fenfluramine, dizocilpine and dextromethorphan, J. Pharmacol. Exp. Ther. 272 (1995) 868-875.

[66] K.T. Finnegan, T. Taraska, Effects of glutamate antagonists on methamphetamine and 3,4-methylenedioxymethamphetamine-induced striatal dopamine release in vivo, J. Neurochem. 66 (1996) 1949-1958.

[67] M.W. Fischman, C.R. Schuster, Tolerance development to chronic methamphetamine intoxication in the rhesus monkey, Pharmacol. Biochem. Behav. 2 (1974) 503-508.

[68] A.E. Fleckenstein, H.M. Haughey, R.R. Metzger, E.L. Kokoshka, E.L. Riddle, J.E. Hanson, J.W. Gibb, G.R. Hanson, Differential effects of psychostimulant agents on dopaminergic and serotonergic transporter function, Eur. J. Pharmacol. 382 (1999) 45-49.

[69] S.E. Friedman, G.K. Castãneda-Hodge, Long-term monoamine depletion, differential recovery and subtle behavioral impairment following methamphetamine-induced neurotoxicity, Pharmacol. Biochem. Behav. 61 (1998) 35-44.

[70] F. Fumagalli, R.R. Gainetdinov, K.J. Valenzano, M.G. Caron, Role of dopamine transporter in methamphetamine-induced neurotoxicity: evidence from mice lacking the transporter, Neuroscience 18 (1998) 4861-4869.

[71] F. Fumagalli, R.R. Gainetdinov, Y.M. Wang, K.J. Valenzano, G.W. Miller, M.G. Caron, Increased methamphetamine neurotoxicity in heterozygous vesicular monoamine transporter 2 knockout mice, J. Neurosci. 19 (1999) 2424-2431.

[72] R.R. Gainetdinov, F. Fumagalli, Y.M. Wang, S.R. Jones, A.I. Levey, G.W. Miller, M.G. Caron, Increased MPTP neurotoxicity in vesicular monoamine transporter 2 heterozygote knockout mice, J. Neurochem. 70 (1998) 1973-1978.

[73] F. Galiyas, L. Zaborszky, J.R. Wolff, Experimental studies of mechanisms involved in methods demonstrating axonal and terminal degeneration, Stain Technol. 55 (1980) 281-290.

[74] D.L. Gelowitz, I.A. Paterson, Neuronal sparing and behavioral effects of the antiapoptotic drug, (—) deprenyl, following kainic acid administration, Pharmacol. Biochem. Behav. 62 (1999) 255-262.

[75] J.W. Gibb, M. Johnson, G.R. Hanson, MK-801 attenuates the methamphetamine induced in tryptophan hydroxylase activity, NIDA Res. Monogr. 95 (1989) 511.

[76] K. Golembiowska, A. Zylewska, Agonists of Al and A2A adenosine receptors attenuate methamphetamine-induced overflow of dopamine in rat striatum, Brain Res. 806 (1998) 202-209.

[77] P.F. Good, A. Hsu, D.P. Werner, P. Perl, C.W. Olanow, Protein nitration in Parkinson's disease, J. Neuropathol. Exp. Neurol. 57 (1998) 338-342.

[78] A. Gow, D. Duran, S.R. Thom, H. Ischiropoulos, Carbon dioxide enhancement of peroxynitrite-mediated protein tyrosine nitration, Arch. Biochem. Biophys. 333 (1996) 42-48.

[79] AJ. Gow, S.R. Thom, H. Ischiropoulos, Nitric oxide and perox-

ynitrite-mediated pulmonary cell death, Am. J. Physiol. 274 (1998) L112-L118.

[80] A.J. Gow, R. Foust III, M. McClelland, S. Malcolm, H. Ischiropoulos (, Pathophysiological reactivities of nitric oxide, in: Y. Ishimura, H. Shimada, M. Suematsu (Eds.), Keio University Symposia for Life Science and Medicine, Oxygen Homeostasis and Its Dynamics, Springer-Verlag, Tokyo, 1998, pp. 493-504.

[81] A.J. Gow, Q. Chen, M. Gole, M. Themistocleous, V.M. Lee, H. Ischiropoulos, Two distinct mechanisms of nitric oxide-mediated neuronal cell death show thiol dependency, Am. J. Physiol. Cell Physiol. 278 (2000) C1099-C1107.

[82] D.G. Graham, S.M. Tiffany, W.R. Bell, W.F. Gutknecht, Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine and related compounds toward C-1300 neuroblastoma cells in vitro, Mol. Pharmacol. 14 (1978) 644-653.

[83] E.D. Hall, P.K. Andrus, J.A. Oostveen, J.S. Althaus, P.F. Von Voigtlander, Neuroprotective effects of the dopamine D2/D3 agonist pramipexole against postischemic or methamphetamine-induced degeneration of nigrostriatal neurons, Brain Res. 742 (1996) 80-88.

[84] D.E. Hallahan, E. Dunphy, S. Virudachalam, V.P. Sukhatme, D.W. Kufe, R.R. Weichselbaum, c-jun and Egr-1 participate in DNA synthesis and cell survival in response to ionizing radiation exposure, J. Biol. Chem. 270 (1995) 30303-30309.

[85] T.G. Hastings, D.A. Lewis, MJ. Zigmond, Role of oxidation in the neurotoxic effects of intrastriatal dopamine injections, Proc. Natl. Acad. Sci. USA 93 (1996) 956-961.

[86] T. Hayashi, L.I. Tsao, J.L. Cadet, T.P. Su, [D-Ala2, D-Leu5] enkephalin blocks the methamphetamine-induced c-fos mRNA increase in mouse striatum, Eur. J. Pharmacol. 366 (1999) R7-R8.

[87] S.J. Heales, J.P. Bolanos,V.C. Stewart, P.S. Brookes, J.M. Land, J.B. Clark, Nitric oxide, mitochondria and neurological disease, Biochem. Biophys. Acta 1410 (1999) 215-228.

[88] T. Herdegen, J.D. Leah, Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins, Brain Res. Brain Res. Rev. 28 (1998) 370-490.

[89] B.E. Hetzler, H.K. Burkard, Effects of dizocilpine (MK-801) on flash-evoked potentials, body temperature, and locomotor activity of hooded rats, Pharmacol. Biochem. Behav. 62 (1999) 559-573.

[90] H.H. Hirata, B. Ladenheim, E. Carlson, C. Epstein, J.L. Cadet, Autoradiographic evidence for methamphetamine-induced striatal dopaminergic loss in mouse brain; attenuation in CuZu-superoxide dismutase transgenic mice, Brain Res. 714 (1996) 95-103.

[91] H. Hirata, M. Asanuma, J.L. Cadet, Melatonin attenuates methamphetamine-induced toxic effects on dopamine and serotonin terminals in mouse brain, Synapse 30 (1998) 150-155.

[92] H. Hirata, M. Asanuma, J. Cadet, Superoxide radicals are mediators of the effects of methamphetamine on Zif268 (Egr-1, NCFI-A) in the brain: evidence from using CuZn superoxide dismutase transgenic mice, Brain Res. Mol. Brain Res. 58 (1998) 209-216.

[93] E.C. Hirsch, B.A. Faucheux, Iron metabolism and Parkinson's disease, Mov. Disord. 3 (1998) 39-45.

[94] A.J. Hotchkiss, J.W. Gibb, Long-term effects of multiple doses of methamphetamine on tryptophan hydroxylase and tyrosine hydroxylase activity in the rat brain, J. Pharmacol. Exp. Ther. 214 (1980) 257-262.

[95] M.D. Huang, FJ. Wan, CJ. Tseng, C.S. Tung, Nicotinamide attenuates methamphetamine-induced striatal dopamine depletion in rats, NeuroReport 8 (1997) 1883-1885.

[96] S.Z. Imam, G.D. Newport, F. Islam, W. Slikker Jr., S.F. Ali, Selenium, an antioxidant, protects against methamphetamine-induced dopaminergic neurotoxicity, Brain Res. 818 (1999) 575-578.

[97] S.Z. Imam, S.F. Ali, Selenium, an antioxidant, attenuates methamphetamine-induced dopaminergic toxicity and peroxynitrite generation, Brain Res. 855 (2000) 186-191.

[98] Y. Ishida, K. Todaka, I. Kuwahara, H. Hashiguchi, Y. Ishizuka, H. Nakane, Y. Mitsuyama, Peripherally administered tetrahydrobiopterin increases in vivo tryptophan hydroxylase activity in the striatum after transplantation of fetal ventral mesencephalon in six hydroxydopamine lesioned rats, Neurosci. Lett. 253 (1998) 45-48.

[99] Y. Itzhak, S.F. Ali, The neuronal nitric oxide synthase inhibitor, 7-nitroindazole, protects against methamphetamine-induced neurotoxicity in vivo, J. Neurochem. 67 (1996) 1770-1773.

[100] Y. Itzhak, C. Gandia, PL. Huang, S.F. Ali, Resistance of neuronal nitric oxide synthase-deficient mice to methamphetamine-induced dopaminergic neurotoxicity, J. Pharmacol. Exp. Ther. 284 (1998) 1040-1047.

[101] J. Jaffe, Amphetamine (or amphetamine-like)-related disorders, in: H.I. Kaplan, B.J. Sadock (Eds.), Comprehensive Textbook of Psychiatry, Williams and Wilkins, Baltimore, 1995, pp. 791-799.

[102] S. Jayanthi, B. Ladenheim, J.L. Cadet, Methamphetamine-induced changes in antioxidant enzymes and lipid peroxidation in copper/zinc-superoxide dismutase transgenic mice, Ann. N.Y. Acad. Sci. 844 (1998) 92-102.

[103] X.R. Jiang, M.Z. Wrona, G. Dryhurst, Tryptamine-4,5-dione, a putative endotoxic metabolite of the superoxide-mediated oxidation of serotonin, is a mitochondrial toxin: possible implications in neurodegenerative brain disorders, Chem. Res. Toxicol. 12 (1999) 429-436.

[104] M. Johnson, G.R. Hanson, J.W. Gibb, Effect of MK-801 on the decrease in tryptophan hydroxylase induced by methamphetamine and its methylenedioxy analog, Eur. J. Pharmacol. 165 (1989) 315-318.

[105] R.S. Johnson, B.M. Spiegelman,V. Papaioannou, Pleiotropic effects of a null mutation in the c-fos proto-oncogene, Cell 71 (1992) 577-586.

[106] H. Kalant, O.J. Kalant, Death in amphetamine users: causes and rates, Can. Med. Assoc. J. 112 (1975) 299-304.

[107] Y. Katz, R. Weizman, A. Weizman, M. Gayish, Disulfiram and diethyldithiocarbamate are competitive inhibitors at the peripheral benzodiazepine receptor, J. Pharmacol. Exp. Ther. 262 (1992) 394-397.

[108] M. Keim, R. Dahmann, D. Wink, M. Feelisch, The nitric oxide/superoxide assay. Insights into the biological chemistry of the NO/O-2 interaction, J. Biol. Chem. 272 (1997) 9922-9932.

[109] H.C. Kim, W.K. Jhoo, D.Y. Choi, D.H. Im, E.J. Shin, J.H. Suh, R.A. Floyd, G. Bing, Protection of methamphetamine nigrostriatal toxicity by dietary selenium, Brain Res. 851 (1999) 76-86.

[110] M.S. Kleven, L.S. Seiden, Methamphetamine-induced neurotoxicity: structure activity relationships, Ann. N.Y. Acad. Sci. 654 (1992) 292-301.

[111] R.A. Koeppe, K.A. Frey, T.M. Vander-Broght, A. Karlamangla, D.M. Jewett, L.C. Lee, M.R. Kiboum, D.E. Kuhl, Kinetic evaluation of [^{n}C] dihydrotetrabenazine by dynamic PET: measurement of vesicular monoamine transporter, J. Cereb. Blood Flow Metab. 16 (1996) 1288-1299.

[112] J.M. Kokoshka, A.E. Fleckenstein, D.G. Wilkins, G.R. Hanson, Age-dependent differential responses of monoaminergic systems to high doses of methamphetamine, J. Neurochem. 75 (2000) 2095-2102.

[113] K. Konuma, Use and abuse of amphetamine in Japan, in: A.K. Cho, D.S. Segal (Eds.), Amphetamine and Its Analogs, Academic Press, San Diego, CA, 1994, pp. 415-438.

[114] W.H. Koppenol, J.J. Moreno, W.A. Pryor, H. Ischiropoulos, J.S. Beckman, Peroxynitrite, a cloaked oxidant formed by nitric oxide and superoxide, Chem. Res. Toxicol 5 (1992) 834-842.

[115] K. Koshimura, J. Tanaka, Y. Murakami, Y. Kato, Enhancement of neuronal survival by 6R-tetrahydrobiopterin, Neuroscience 88 (1999) 561-569.

[116] B.E. Kosofsky, M.E. Molliver, The serotoninergic innervation of cerebral cortex: different classes of axon terminals arise from dorsal and median raphe nuclei, Synapse 1 (1997) 153-168.

[117] P. Kotsonis, L.G. Frohlich, ZV. Shutenko, R. Horejsi,W. Pfleiderer,

H. H. Schmidt, Allosteric regulation of neuronal nitric oxide synthase by tetrahydrobiopterin and suppression of auto-damaging superoxide, J. Biochem. 346 (2000) 767-776.

[118] J.C. Kramer, V.S. Fischman, D.C. Littlefield, Amphetamine abuse: pattern and effects of high doses taken intravenously, J. Am. Med. Assoc. 201 (1967) 305-309.

[119] I. Kurkowska-Jastrzebska, A. Wronska, M. Kohutnicka, A. Czlonkowska, The inflammatory reaction following l-methyl-4-phenyl-I, 2,3,6-tetrahydropyridine intoxication in mouse, Exp. Neurol. 156 (1999) 50-61.

[120] J.R. Lancaster Jr., A tutorial on the diffusibility and reactivity of free nitric oxide, Nitric Oxide 1 (1997) 18-30.

[121] J.W. Langston, L.S. Fomo, J. Tetrud, A.G. Reeves, J.A. Kaplan, D. Karluk, Evidence of active nerve cell degeneration in the substantia nigra of humans years after l-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exposure, Ann. Neurol. 46 (1999) 598-605.

[122] MJ. LaVoie, T.G. Hastings, Dopamine quinone formation and protein modification associated with the striatal neurotoxicity of methamphetamine: evidence against a role for extracellular dopamine, J. Neurosci. 19 (1999) 1484-1491.

[123] R.T. Layer, L.R. Bland, P. Skolnick, MK-801, but not drugs acting at strychnine-insensitive glycine receptors, attenuate methamphetamine nigrostriatal toxicity, Brain Res. 625 (1993) 38-44.

[124] A. Lecci, F. Borsini, L. Gragnani, G. Volterra, A. Meli, Effect of psychotomimetics and some putative anxiolytics on stress-induced hyperthermia, J. Neural Transm. 83 (1991) 67-76.

[125] J.J. Lemasters, T. Qian, C.A. Bradham, D.A. Brenner, W.E. Cascio, L.C. Trost, Y. Nishimura, A.L. Nieminen, B. Herman, Mitochondrial dysfunction in the pathogenesis of necrotic and apoptotic cell death, J. Bioenerg. Biomembr. 31 (1999) 305-319.

[126] Y. Li, A.K. Jaiswal, Identification of jun-B as a third member in human antioxidant response element-nuclear protein complex, Biochem. Biophys. Res. Commun. 188 (1992) 992-996.

[127] L.P. Liang, S. Kaufman, The regulation of dopamine release from striatum slices by tetrahydrobiopterin and L-arginine-derived nitric oxide, Brain Res. 800 (1998) 181-186.

[128] G.T. Liberatore, V. Jackson-Lewis, S.Vukosavic, A.S. Mandir, M. Vila, W.G. McAuliffe, V.L. Dawson, T.M. Dawson, S. Przedborski, Inducible nitric oxide synthase stimulates dopaminergic neurodegeneration in the MPTP model of Parkinson disease, Nature Med. 5 (1999) 1403-1409.

[129] J.A. Lieberman, B.J. Kinon, A.D. Loebel, Dopaminergic mechanisms in idiopathic and drug-induced psychoses, Schizophr. Bull. 16 (1990) 97-110.

[130] P.S. Lin, S. Quamo, K.C. Ho, J. Gladding, Hyperthermia enhances the cytotoxic effects of reactive oxygen species to Chinese hamster cells and bovine endothelial cells in vitro, Radiat. Res. 126 (1991) 43-51.

[131] S.A. Lipton, P.A. Rosenberg, Excitatory amino acids as a final common pathway for neurologic disorders, New Engl. J. Med. 330 (1994) 613-622.

[132] J.E. Malberg, K.E. Sabol, L.S. Seiden, Co-administration of MDMA with drugs that protect against MDMA neurotoxicity produces different effects on body temperature in the rat, J. Pharmacol. Exp. Ther. 278 (1996) 258-267.

[133] R.K. Mamatha, S.N. Nagendra, Effect of disulfiram administration on glutamate uptake by synaptosomes in the rat brain, Eur. J. Pharmacol. 292 (1994) 89-94.

[134] S. Mankhetom, Z. Abedinzadeh, C. Houee-Levin, Antioxidant action of soduim diethyldithiocarbanate: reaction with hydrogen peroxide and superoxide radical, Free Radic. Biol. 17 (1994) 517-527.

[135] T. Masukawa, K. Nakanishi, Protection by disulfiram and diethyldithiocarbamate against hypoxia-induced lethality in mice, Jap. J. Pharmacol. 63 (1993) 279-284.

[136] B. Mayer, P. Klatt, E.R. Werner, K. Schmidt, Kinetics and mechanism of tetrahydrobiopterin-induced oxidation of nitric oxide, J. Biol. Chem. 270 (1995) 655-659.

[137] U.D. McCann, D.F. Wong, F. Yokoi, V. Villemagne, R.F. Dannals, G.A. Ricuarte, Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [C]WIN-35,428, J. Neurosci. 18 (1998) 8417-8422.

[138] P.L. McGreer, S. Itagaki, H. Akiyama, E.G. McGreer, Rate of cell death in Parkinsonism indicates active neuropathological process, Ann. Neurol. 24 (1988) 574-576.

[139] W.P. Melega, A.E. Williams, D.A. Schmitz, E.W. DiStefano, A.K. Cho, Pharmacokinetic and pharmacodynamic analysis of the actions of D-amphetamine and D-methamphetamine on the dopamine terminal, J. Pharmacol. Exp. Ther. 274 (1995) 90-96.

[140] W.P. Melega, J. Quintana, M.J. Raleigh, D.B. Stout, D.C. Yu, K.P. Lin, S.C. Huang, M.E. Phelps, 6-[18F]fluoro-L-DOPA-PET studies show partial reversibility of long-term effects of chronic amphetamine in monkeys, Synapse 22 (1996) 63-69.

[141] W.P. Melega, MJ. Raleigh, D.B. Stout, S.C. Huang, M.E. Phelps, Ethological and 6-[18F]fluoro-L-DOPA-PET profiles of long-term vulnerability to chronic amphetamine, Behav. Brain Res. 84 (1997) 259-268.

[142] W.P. Melega, G. Lazean, D.C. Harvey, S.C. Huang, M.E. Phelps, Dizocilpine and reduced body temperature do not prevent methamphetamine-induced neurotoxicity in the vervet monkey: [nC]WIN 35,428-positron emission tomography studies, Neurosci. Lett. 258 (1998) 17-20.

[143] W.P. Melega, G. Lazean, A.F. Desalles, M.E. Phelps, Long-term methamphetamine-induced decreases of [nC]WIN 35,428 binding in striatum are reduced by GDNF:PET studies in the Vervet monkey, Synapse 35 (2000) 243-249.

[144] D.B. Miller, J.P. O'callaghan, The interactions of MK-801 with the amphetamine analogues D-methamphetamine (D-Meth), 3,4-methylenedioxymethamphetamine (d-MDMA) or D-fenfluramine (d-FEN): neural damage and neural protection, Ann. N.Y. Acad. Sci. 679 (1993) 321-324.

[145] D.B. Miller, J.P. O'Callaghan, The role of temperature, stress, and other factors in the neurotoxicity of the substituted amphetamines 3,4-methylenedioxymethamphetamine and fenfluramine, Mol. Biol. 11 (1995) 177-192.

[146] GJ. Moffat, A.W. McLaren, C.R. Wolf, Involvement of Jun and Fos proteins in regulating transcriptional activation of the human pi class glutathione S-transferase gene in multidrug-resistant MCF7 breast cancer cells, J. Biol. Chem. 269 (1994) 16397-16402.

[147] R. Moratalla, H.A. Robertson, A.M. Graybiel, Dynamic regulation of NGFI-A (zif268, egrl) gene expression in the striatum, J. Neurosci. 12 (1992) 2609-2622.

[148] T. Morimoto, K. Kida, H. Nagao, K. Yoshida, M. Fukuda, S. Takashima, The pathogenic role of the NMDA receptor in hyperthermia-induced seizures in developing rats, Brain Res. 84 (1995) 204-207.

[149] A. Muraki, T. Koyama, M. Nakayama, T. Ohmori, I. Yamashita, MK-801, a non-competitive antagonist of NMDA receptor prevents methamphetamine-induced decrease of striatal dopamine uptake sites in the rat striatum, Neurosci. Lett. 136 (1992) 39-42.

[150] A.N. Murphy, G. Fiskum, M.F. Beal, Mitochondria in neurodegeneration: bioenergetic function in cell life and death, J. Cereb. Blood Flow Metab. 19 (1999) 231-245.

[151] K. Nakamura, D.A. Wright, T. Wiatr, D. Kowlessur, S. Milstien, X.G. Lei, UJ. Kang, Preferential resistance of dopaminergic neurons to the toxicity of glutathione depletion is independent of cellular glutathione peroxidase and is mediated by tetrahydrobiopterin, J. Neurochem. 74 (2000) 2305-2314.

[152] N. Nakao, K. Nakai, T. Itakura, Metabolic inhibition enhances selective toxicity of l-DOPA toward mesencephalic dopamine neurons in vitro, Brain Res. 777 (1997) 202-209.

[153] J.F. Nash, B.K. Yamamoto, Effect of D-amphetamine on the extracellular concentrations of glutamate and dopamine in iprindole-treated rats, Brain Res. 627 (1993) 1-8.

[154] J.F. Nash, B.K. Yamamoto, Methamphetamine neurotoxicity and striatal glutamate release: comparison to 3,4-methylenedioxymethamphetamine, Brain Res. 58 (1992) 237-243.

[155] J.P. O'Callaghan, D.B. Miller, Neurotoxic effects of substituted amphetamine in rats and mice: challenge to the current dogma, in: E. Massaro, P.A. Broderick (Eds.), Handbook of Neurotoxicity, Vol. 2, Humana Press, New York, 2000.

[156] SJ. O'Dell, F.B. Weihmuller, J.F. Marshall, MK-801 prevents methamphetamine-induced striatal dopamine damage and reduces extracellular dopamine overflow, Ann. N.Y. Acad. Sci. 648 (1992) 317-319.

[157] T. Ohmori, T. Koyama, A. Muraki, I. Yamashita, Competitive and noncompetitive TV-methyl-D-aspartate antagonists protect dopaminergic and serotonergic neurotoxicity produced by methamphetamine in various brain regions, J. Neural Transm. 92 (1993) 97-106.

[158] R.A. Omar, S. Yano, Y. Kikkawa, Antioxidant enzymes and survival of normal and simian virus 40-transformed mouse embryo cells after hyperthermia, Cancer Res. 47 (1987) 3473-3476.

[159] F. Owen, H.F. Baker, R.M. Ridley, A.J. Cross, T.J. Crow, Effect of chronic amphetamine administration on central dopaminergic mechanisms in the vervet, Psychopharmacology 74 (1981) 213—216.

[160] I.A. Paterson, W.G. Tatton, Antiapoptotic actions of monoamine oxidase B inhibitors, Adv. Pharmacol. 42 (1998) 312-315.

[161] P.E. Paulson, T.E. Robinson, Regional differences in the effects of amphetamine withdrawal on dopamine dynamics in the striatum, Neuropsychopharmacology 14 (1996) 325-337.

[162] R.N. Pechnick, C.A. Wong, R. George, A. Thurkauf, A.E. Jacobsen, K.C. Rice, Comparison of the effects of the acute administration of dexoxadrol, levoxadrol, MK-801 and phencyclidine on body temperature in the rat, Neuropharmacology 28 (1989) 829-835.

[163] T.I. Peng, J.T. Greenamyre, Privileged access to mitochondria of calcium influx through V-methyl-D-aspartate receptors, Mol. Pharmacol. 53 (1998) 974-980.

[164] I.L. Petrakis, K.M. Carroll, C. Nich, L.T. Gordon, E.F. McCance-Katz, T. Frankforter, B.J. Rounsaville, Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts, Addiction 95 (2000) 219-228.

[165] R. Pinkus, L.M. Weiner, V. Daniel, Role of quinone-mediated generation of hydroxyl radicals in the induction of glutathione S-transferase gene expression, Biochemistry 34 (1995) 81-88.

[166] K.L. Preston, G.C. Wagner, C.R. Schuster, L.S. Seiden, Long-term effects of repeated methylamphetamine administration on monoamine neurons in the rhesus monkey brain, Brain Res. 338 (1985) 243-248.

[167] S. Przedborski, V. Jackson-Lewis, R. Yokoyama, T. Shibata, V.L. Dawson, T.M. Dawson, Role of neuronal nitric oxide in 1-methyl-4-phenyl-l,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurotoxicity, Proc. Natl. Acad. Sci. USA 93 (1996) 4565-4571.

[168] C. Pu, J.E. Fisher, G.D. Cappon, C.V. Vorhees, The effects of amfonelic acid, a dopamine uptake inhibitor, on methamphetamine-induced dopaminergic terminal degeneration and astrocytic response in rat striatum, Brain Res. 649 (1994) 217-224.

[169] C. Pu, CV. Vorhees, Protective effects of MK-801 on methamphetamine-induced depletion of dopaminergic and serotonergic terminals and striatal astrocytic response: an immunohistochemical study, Synapse 19 (1995) 97-104.

[170] O. Pucilowski, W. Danysz, D.H. Overstreet, A.H. Rezvani, B. Eichelman, D.S. Janowsky, Decreased hyperthermia effect of MK-801 in selectively bred hypercholinergic rats, Brain Res. Bull. 26 (1991) 621-625.

[171] J.F. Reinhard, A.J. Daniels, O.H. Viveros, Potentiation by reserpine and tetra-benozine of brain catecholamine depletion by MPTP in the mouse: evidence for subcellular sequestration as a basis for cellular resistance to the toxicant, Neurosci. Lett. 90 (1988) 349-353.

[172] G.A. Ricaurte, C.R. Schuster, L.S. Seiden, Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: a regional study, Brain Res. 193 (1980) 153-163.

[173] G.A. Ricaurte, R.W. Guillery, L.S. Seiden, C.R. Schuster, R.Y. Moore, Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain, Brain Res. 235 (1982) 93-103.

[174] G.A. Ricaurte, L.S. Seiden, C.R. Schuster, Further evidence that amphetamine produced long lasting dopamine neurochemical deficits by destroying dopamine nerve fibers, Brain Res. 303 (1984) 358-364.

[175] G.A. Ricaurte, K.E. Sabol, L.S. Seiden, Functional consequences of neurotoxic amphetamine exposure, in: A.K. Cho, D.S. Segal (Eds.), Amphetamine and Its Analogs: Psychopharmacology, Toxicology and Abuse, Academic Press, San Diego, 1994, pp. 297-313.

[176] J.L. Ridet, S.K. Malhotra, A. Privat, F.H. Gage, Reactive astrocytes: cellular and molecular cues to biological function, Trends Neurosci. 20 (1997) 570-577.

[177] R.M. Ridley, H.F. Baker, F. Owen, A.J. Cross, TJ. Crow, Behavioral and biochemical effects of chronic amphetamine treatment in the vervet monkey, Psychopharmacology 78 (1982) 245-251.

[178] T.E. Robinson, J. Yew, P.E. Paulson, D.M. Camp, The long-term effects of neurotoxic doses of methamphetamine on the extracellular concentration of dopamine measured with microdialysis in striatum, Neurosci. Lett. 220 (1990) 293-298.

[179] R.B. Rothman, J.S. Partilla, M.H. Baumann, C.M. Dersch, F.I. Carroll, K.C. Rice, Neurochemical neutralization of methamphetamine with high affinity nonselective inhibitors of biogenic amine transporters:a pharmacological strategy for treating stimulant abuse, Synapse 35 (2000) 222-227.

[180] LJ. Ryan, J.C. Linder, M.E. Martone, P.M. Groves, Histological and ultrastructural evidence that D-amphetamine causes degeneration in the neostriatum frontal cortex of rats, Brain Res. 518 (1990) 67-77.

[181] V. Sandoval, G.R. Hanson, A.E. Fleckenstein, Methamphetamine decreases mouse striatal dopamine transporter activity: roles of hyperthermia and dopamine, Eur. J. Pharmacol. 409 (2000) 265-271.

[182] H. Sawada, M. Ibi, T. Kihara, M. Urushitani, A. Akaike, J. Kimura, S. Shimohama, Dopamine D2-type agonists protect mesencephalic neurons from glutamate neurotoxicity: mechanisms of neuroprotective treatment against oxidative stress, Ann. Neurol. 44 (1998) 110-119.

[183] C.J. Schmidt, J.W. Gibb, Role of the serotonin uptake carrier in the neurochemical response to methamphetamine: effects of citalopram and chloroimipramine, Neurochem. Res. 10 (1985) 637-684.

[184] L.C. Schmued, J.F. Bowyer, Methamphetamine exposure can produce neuronal degeneration in mouse hippocampal remnants, Brain Res. 759 (1997) 135-140.

[185] L.S. Seiden, R.C. MacPhail, M.W. Oglesby, Catecholamines and drug-behavior interactions, Fed. Proc. 34 (1975) 1823-1831.

[186] L.S. Seiden, G.A. Ricaurte, Neurotoxicity of methamphetamine and related drugs, in: H.Y. Meltzer (Ed.), Psychopharmacology: The Third Generation of Progress, Raven Press, New York, 1987, pp. 359-366.

[187] L.S. Seiden, K.E. Sabol, G.A. Ricaurte, Amphetamine: effects on catecholamine systems and behavior, Annu. Rev. Pharmacol. Toxicol. 33 (1993) 639-677.

[188] L.S. Seiden, K.E. Sabol, Methamphetamine and methylenedioxymethamphetamine neurotoxicity: possible mechanisms of cell destruction, NIDA Res. Monogr. 163 (1996) 251-276.

[189] P. Sheng, B. Ladenheim, T.H. Moran, X.B. Wang, J.L. Cadet, Methamphetamine-induced neurotoxicity is associated with increased striatal AP-1 DNA-binding activity in mice, Brain Res. Mol. Brain Res. 42 (1996) 171-174.

[190] P. Sheng, C. Cerruti, S. Ali, J.L. Cadet, Nitric oxide is a mediator of methamphetamine (METH)-induced neurotoxicity. In vitro evidence from primary cultures of mesencephalic cells, Ann. N.Y. Acad. Sci. 80 (1996) 174-186.

[191] F. Shibata, A. Baird, R.Z. Florkiewicz, Functional characterization of the human basic fibroblast growth factor gene promoter, Growth Factors 4 (1991) 277-287.

[192] S. Shimizu, M. Ishii, K. Momose, T. Yamamoto, Role of tetrahydrobiopterin in the function of nitric oxide synthase, and its cytoprotective effect, Int. J. Mol. Med. 2 (1998) 533-540.

[193] J.L. Skibba, R.H. Powers, A. Stadnicka, D.W. Cullinane, U.A. Almagro, J.H. Kalbfleisch, Oxidative stress as a precursor to the irreversible hepatocellular injury caused by hyperthermia, Int. J. Hyperthermia 7 (1991) 749-761.

[194] P.K. Sonsalla, WJ. Nicklas, R.E. Heikkila, Role for excitatory amino acids in methamphetamine-induced dopaminergic toxicity, Science 243 (1989) 398-400.

[195] P.K. Sonsalla, D.F. Riordan, R.E. Heikkila, Competitive and noncompetitive antagonist at A-methyl-o-aspartate receptors protect against methamphetamine-induced dopaminergic damage in mice, J. Pharmacol. Exp. Ther. 256 (1991) 506-512.

[196] P.K. Sonsalla, M.D. Jochnowitz, G.D. Zeevalk, J.A. Oostveen, E.D. Hall, Treatment of mice with methamphetamine produces cell loss in the substantia nigra, Brain Res. 738 (1996) 172-175.

[197] P.K. Sonsalla, D.S. Albers, G.D. Zeevalk, Role of glutamate in neurodegenerative of dopamine neurons in several animal models of parkinsonism, Amino Acids 14 (1998) 69-74.

[198] M.B. Spina, G. Cohen, Dopamine turnover and glutathione oxidation: implications for Parkinson disease, Proc. Natl. Acad. Sci. USA 86 (1989) 1398-1400.

[199] S.E. Stephans, B.K. Yamamoto, Methamphetamine-induced neurotoxicity: roles for glutamate and dopamine efflux, Synapse 17 (1994) 203-209.

[200] S.E. Stephans, T.S. Whittingham, A.J. Douglas, W.D. Lust, B.K. Yamamoto, Substrates of energy metabolism attenuate methamphetamine-induced neurotoxicity in striatum, J. Neurochem. 71 (1998) 613-621.

[201] M.A. Stevenson, S.K. Calderwood, G.M. Hahn, Rapid increases in inositol trisphosphate and intracellular Ca^{2+} after heat shock, Biochem. Biophys. Res. Commun. 137 (1986) 826-833.

[202] M.A. Stevenson, S.K. Calderwood, G.M. Hahn, Effect of hyperthermia (45 degrees C) on calcium flux in Chinese hamster ovary HA-1 fibroblasts and its potential role in cytotoxicity and heat resistance, Cancer Res. 47 (1987) 3712-3717.

[203] A.K. Stout, H.M. Raphael, B. I Kanterewicz, E. Klann, I.J. Reynolds, Glutamate-induced neuron death requires mitochondrial calcium uptake, Nature Neurosci. 1 (1998) 366-373.

[204] T.P. Su, Delta opioid peptide [D-Ala(2)J)-Leu(5)] enkephalin promotes cell survival, J. Biomed. Sci. 7 (2000) 195-199.

[205] N. Takahashi, L.L. Miner, I. Sora, H. Ujike, R.S. Revay,V. Kostic, V. Jackson-Lewis, S. Przedborski, G.R. Uhl, $vMAT_2$ knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion and enhanced MPTP toxicity, Proc. Natl. Acad. Sci. USA 94 (1997) 9938-9943.

[206] W.G. Tatton, R.M. Chalmers-Redman, Mitochondria in neurodegenerative apoptosis: an opportunity for therapy?, Ann. Neurol. 44 (1998) S134-S141.

[207] F. Torreilles, S. Salman-Tabecheh, M.C. Guérin, J. Torreilles, Neurodegenerative disorders: the role of peroxynitrite, Brain Res. Rev. 30 (1999) 153-163.

[208] L.I. Tsao, B. Ladenheim, A.M. Andrews, C.C. Chiueh, J.L. Cadet, T.P. Su, Delta opioid peptide [D-Ala2J)-leu5] enkephalin blocks the long-term loss of dopamine transporters induced by multiple administrations of methamphetamine: involvement of opioid receptors and reactive oxygen species, J. Pharmacol. Exp. Ther. 287 (1998) 322-331.

[209] L.I. Tsao, J.L. Cadet, T.P. Su, Reversal by [D-Ala2JD-Leu5] enkephalin of the dopamine transporter loss caused by methamphetamine, Eur. J. Pharmacol. 372 (1999) R5-R7.

[210] A. Vaccari, L. Ferraro, P. Saba, S. Ruiu, I. Mocci, T. Antonelli, S. Tanganelli, Differential mechanisms in the effects of disulfiram and diethyldithiocarbamate intoxication on striatal release and vesicular, J. Pharmacol. Exp. Ther. 285 (1998) 961-967.

[211] V. Villemagne, J. Yuan, D.F. Wong, R.F. Dannals, G. Hatzidimitriou, W.B. Mathews, H.T. Ravert, J. Musachio, U.D. McCann, G.A. Ricaurte, Brain dopamine neurotoxicity in baboons treated with doses of methamphetamine comparable to those recreationally abused by humans: evidence from [^{n}C]WIN 35,428 positron emission tomography studies and direct in vitro determinations, J. Neurosci. 18 (1998) 419-427.

[212] F.J. Vingerhoets, R.J. Uitti, D.B. Caine, Deprenyl and the issue of neuroprotection, Eur. J. Neurol. 34 (1994) 1-3.

[213] N.D. Volkow, L. Chang, G.J. Wang, J.S. Fowler, D. Franceschi, MJ. Sedler, SJ. Gatley, R. Hitzemann, Y.S. Ding, C. Wong, J. Logan, Higher cortical and lower subcortical metabolism in detoxified methamphetamine abusers, Am. J. Psychol. 158 (2001) 383-389.

[214] N.D. Volkow, L. Chang, GJ. Wang, J.S. Fowler, M. Leonido-Yee, D. Franceschi, MJ. Sedler, S J. Gatley, R. Hitzemann, Y.S. Ding, J. Logan, C. Wong, E.N. Miller, Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers, Am. J. Psychol. 158 (2001) 377-382.

[215] G.C. Wagner, R.M. Carelli, MJ. Jarvis, Pretreatment with ascorbic acid attenuates the neurotoxic effects of methamphetamine in rats, Res. Commun. Chem. Pathol. Pharmacol. 47 (1985) 221-228.

[216] G.C. Wagner, S.L. Walsh, Evaluation of the effects of inhibition of monoamine oxidase and senescence on methamphetamine-induced neuronal damage, Int. J. Dev. Neurosci. 9 (1991) 171-174.

[217] FJ. Wan, H.C. Lin, Y.S. Lin, CJ. Tseng, Intra-striatal infusion of D-amphetamine induces hydroxyl radical formation: inhibition by MK-801 pretreatment, Neuropharmacology 39 (2000) 419-426.

[218] Z.Q. Wang, C. Ovitt, A.E. Grigoriadis, U. Mohle-Steinlein, U. Ruther, E.F. Wagner, Bone and haematopoietic defects in mice lacking c-fos, Nature 360 (1992) 741-745.

[219] J.Q. Wang, J.B. Daunais, J.F. McGinty, Role of kainate/AMPA receptors in induction of striatal zif/268 and preprodynorphin mRNA by a single injection of amphetamine, Brain Res. Mol. Brain Res. 27 (1994) 118-126.

[220] Q. Wei, O.P. Jurma, J.K. Andersen, Increased expression of monoamine oxidase-B results in enhanced neurite degeneration in methamphetamine-treated PC 12 cells, J. Neurosci. Res. 50 (1997) 618-626.

[221] F.B. Weihmuller, SJ. O'Dell, J.F. Marshall, MK-801 protection against methamphetamine-induced striatal dopamine terminal injury is associated with attenuated dopamine overflow, Synapse 11 (1992) 155-163.

[222] J.M. Wilson, A.I. Levey, A. Rajput, L. Ang, M. Guttman, K. Shannak, H.B. Niznik, O. Homykiewicz, C. Pifl, SJ. Kish, Differential changes in neurochemical markers of striatal dopamine nerve terminals in idiopathic Parkinson's disease, Neurology 47 (1996) 718-726.

[223] J.M. Wilson, K.S. Kalasinsky, A.I. Levey, C. Bergeron, G. Reiber, R.M. Anthony, G.A. Schmunk, K. Shannak, J.W. Haycock, SJ. Kish, Striatal dopamine nerve terminal markers in human, chronic methamphetamine users, Nature Med. 2 (1996) 699-703.

[224] D.A. Wink, J.B. Mitchell, Chemical biology of nitric oxide: insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide, Free Radic. Biol. Med. 25 (1998) 434-456.

[225] W.L. Woolverton, G.A. Ricaurte, L.S. Fomo, L.S. Seiden, Long-term effects of chronic methamphetamine administration in rhesus monkeys, Brain Res. 486 (1989) 73-78.

[226] M.Z. Wrona, G. Dry hurst, Oxidation of serotonin by superoxide radical: implications to neurodegenerative brain disorders, Chem. Res. Toxicol. 11 (1998) 639-650.

[227] Y.T. Xuan, X.L. Tang, S. Banerjee, H. Takano, R.C. Li, H. Han, Y. Qiu, J J. Li, R. Bolli, Nuclear factor-kappaB plays an essential role in the late phase of ischemic preconditioning in conscious rabbits, Circulation Res. 84 (1999) 1095-1109.

[228] B.K. Yamamoto, W. Zhu, The effects of methamphetamine on the production of free radicals and oxidative stress, J. Pharmacol. Exp. Ther. 287 (1998) 107-114.

[229] E.D.G. Zalis, L.F. Parmley, Fatal amphetamine poisoning, Arch. Intern. Med. 112 (1963) 60-64.

[230] X.H. Zhong, J.W. Haycock, K. Shannak, Y. Robitaille, J. Fratkin, A.H. Koeppen, O. Hornykiewicz, S.J. Kish, Striatal dihydroxyphenylalanine decarboxylase and tyrosine hydroxylase protein in idiopathic Parkinson's disease and dominantly inherited olivopontocerebellar atrophy, Mov. Disord. 101 (1995) 10-17.