

# Clinical physiology and mechanism of dizocilpine (MK-801)

## Electron transfer, radicals, redox metabolites and bioactivity

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**Key words:** dizocilpine (MK-801), mechanism, redox metabolites, radicals, bioactivity

**Abbreviations:** ET, electron transfer; ROS, reactive oxygen species; OS, oxidative stress; AO, antioxidant; PCP, phencyclidine; GSH, glutathione; IDPN, 3,3'-iminodipropionitrile; CAPE, caffeic acid phenethyl ester; NMDA, N-methyl-D-aspartate; CNS, central nervous system; SO, superoxide; Glu, glutamate; GABA, gamma-aminobutyric acid; COX-2, cyclooxygenase-2

Dizocilpine (MK-801), an extensively investigated drug possessing secondary amine and benzenoid functions, displays a wide array of biological properties, including anticonvulsant and anesthetic. There is scant discussion of biomechanism. A relevant, important finding is formation of oxidative metabolites in the hydroxylamine and phenolic categories. Analogy to cocaine metabolites suggests participation of redox entities, such as, hydroxylamine, nitroxide and nitrosonium, which can lead to electron transfer and radical formation. There is also similarity to metabolism by 3,3'-iminodipropionitrile and phencyclidine. Alternatively, the phenolic metabolites are well-known precursors of ET quinones. The review documents various physiological effects, mainly involving the central nervous system. Also of interest are the pro- and anti-oxidant properties. Considerable attention has been paid to MK-801 as an antagonist of the N-methyl-D-aspartate receptor in the glutamate category. This aspect is often associated with effects on the central nervous system. The review also provides recent literature dealing with MK-801/NMDA receptor in various areas of bioactivity. Studies were made of MK-801 involvement in working memory processing. Deficits in behavior were noted after administration of the drug. Treatment of mice with dizocilpine induced learning impairment. The influence of MK-801 on fear has been investigated. The substance is known to exert an analgesic effect in pain control. A number of reports deal with anesthetic properties.

### Introduction

Dizocilpine (MK-801) (1) is an antagonist of the N-methyl-D-aspartate receptor in the glutamate category involved with the central nervous system (CNS). The drug displays a variety of physiological actions, many of which involve the CNS, such as

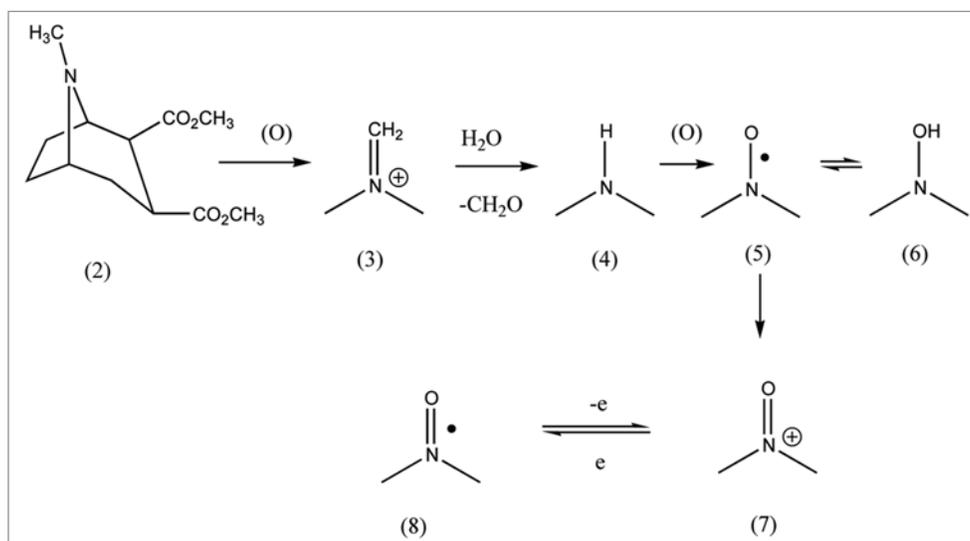
anesthetic and anticonvulsant properties. The bioactivity is discussed within the framework of a unifying mechanistic theme which has been discussed in prior reviews.

The preponderance of bioactive substances and their metabolites incorporate electron transfer (ET) functionalities, which, we believe, play an important role in physiological responses. The main groups include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). In vivo redox cycling with oxygen can occur giving rise to oxidative stress (OS) through generation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkylperoxides, and diverse radicals [hydroxyl, alkoxy, hydroperoxyl and superoxide (SO)]. In some cases, ET results in interference with normal electrical effects, e.g., in respiration or neurochemistry. Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, i.e., more positive than -0.5 V. ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins, e.g., anti-infective agents,<sup>1</sup> anticancer drugs,<sup>2</sup> carcinogens,<sup>3</sup> reproductive toxins,<sup>4</sup> nephrotoxins,<sup>5</sup> hepatotoxins,<sup>6</sup> cardiovascular toxins,<sup>7</sup> nerve toxins,<sup>8</sup> mitochondrial toxins,<sup>9</sup> abused drugs,<sup>10</sup> ototoxins,<sup>11</sup> pulmonary toxins,<sup>12</sup> immune system toxins<sup>13</sup> and various other categories of drugs and toxins, including human illnesses.<sup>14</sup>

There is a plethora of experimental evidence supporting the OS theoretical framework, including generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of antioxidants (AOs), and DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is in keeping with the frequent observations that many ET substances display a variety of activities, e.g., multiple drug properties, as well as toxic effects. Knowledge of events at the molecular level can result in practical application in medicine.

It is instructive to examine the basic biochemistry of ET functionalities in more detail. Redox cycling occurs between hydroquinone and p-benzoquinone, and between catechol and

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**Scheme 1.** Cocaine metabolism. There is similarity to MK-801 in relation to involvement of a secondary-amine (4) with subsequent metabolism to a hydroxylamine (6). Various studies also report participation of nitroxide (3) and nitrosonium (7). There is evidence for redox cycling entailing ET process with subsequent formation of ROS in some cases. The CNS may be involved in the ET reactions. Toxicity might reflect harmful effects from ROS generation.

o-benzoquinone with generation of superoxide via ET to oxygen. Semiquinones act as intermediates. Various amino acids can operate as electron donors. Superoxide serves as precursor to a variety of other ROS. The quinones can belong in either the endogenous or exogenous category. In the case of aromatic nitro compounds, the reduced nitroso and hydroxylamine metabolites can similarly enter into redox cycling, including an oxy radical intermediate. This class is only in the exogenous group and is related to MK-801 metabolism. Less known are conjugated iminium compounds, of which paraquat is a predominant member.

This review demonstrates that the ET-ROS-OS unifying theme, which has been successful for many other classes of drugs and toxins, can also be applied to MK-801 which is a bicyclic secondary amine. Various biochemical properties of the drug are addressed, based on the ET-ROS-OS perspective. The in vivo activities include anesthetic, anticonvulsant, interaction in the brain, neurotoxicity, neuro protection, interaction with abused drugs, motor effects, receptor interaction, behavior, learning and memory. Metabolic evidence points to two main routes whereby ET may be induced, namely, hydroxylamine and phenol formation. Hydroxylamines can undergo redox interactions involving nitroxides and nitrosonium (oxoammonium) species. Analogy is provided based on similar transformations with cocaine, 3,3'-iminodipropionitrile, and phenylhydroxylamine. The phenolic metabolites are well known precursors of ET quinones. Also, receptors and pro- and anti-oxidant actions are treated.<sup>15</sup>

However, it should be emphasized that physiological activity of endogenous and exogenous substances is often complex and multifaceted. Our objective does not encompass extensive treatment of other modes of action. The citations are usually representative, rather than exhaustive. A number of original references may be found in the reviews and articles cited.

### Cocaine Metabolism<sup>16</sup>

These data provide insight concerning MK-801 mechanism. Cocaine (2) is mainly metabolized by two distinct pathways in humans.<sup>17</sup> The major transformation consists of hydrolysis of the ester groups, which is apparently not important in the toxic manifestations. The minor route (**Scheme 1**) is an oxidative one involving the amine moiety, which has attracted most attention relative to some toxic responses. Possible metabolites participating in the effects of (2), in addition to the drug itself, are norcocaine (4), norcocaine nitroxide (5), N-hydroxynorcocaine (6), norcocaine nitrosonium (7), cocaine iminium (3), and formaldehyde.

Oxidative metabolism of (2) yields norcocaine (4), evidently via the iminium derivative (3).<sup>17</sup> Microsomes in the brain and liver further oxidize (4) to the nitroxide (5). This radical is stabilized by delocalization over O and N, and apparently by intramolecular interaction with n-electrons on the ester substituent. The transannular effect which has ample precedent, might well apply to other radical species involved in redox cycling in the cocaine system, as well as to magnitude of the reduction potential.

Another metabolite is the N-hydroxy derivative (5) (a hydroxylamine) which arises from (4) by a sequence comprising electron and proton uptake in reversible manner. The duo of (4) and (5) apparently operates as a couple.<sup>17,18</sup> This system bears resemblance to the one comprising aromatic nitroso compounds (ArNO)-aromatic hydroxylamine (ArNHOH) which redox cycles with participation of the ArNHO· radical.<sup>3</sup>

An alternate redox cycle entails electron loss by (5) to form nitrosonium cation (7) (oxoammonium) reversibly. Which could redox cycle with (8). This aspect has been the object of less attention.

There have been numerous examples concerning involvement of iminiums in drug or toxic action by way of ET-OS.<sup>1-5</sup> Bioactive

*tert*-amines are believed to be widespread source of this functionality.<sup>19</sup> Application to cocaine was made in 1988,<sup>17</sup> followed more recently by speculation that long-term exposure to cyclic *tert*-amines, such as cocaine, may result in biochemical lesions via reactive metabolites, e.g., iminium types, thought to be primarily responsible for neurotoxicity.<sup>20</sup> Usually, iminiums that participate in ET are conjugated types.<sup>1-5</sup> Exceptions appear to be those that attain stabilization of the derived radical by intramolecular interaction with n-electrons, as in the case of cocaine or phencyclidine (PCP).<sup>21</sup>

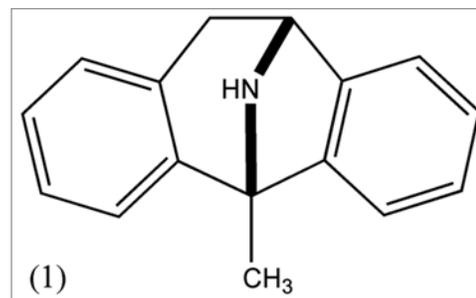
Although electrochemistry can provide valuable mechanistic insight, unfortunately, it has received little attention in the medicinal chemistry area. If the reduction potential is more positive than -0.5 V, then there is the possibility of ET in the biological domain. Electrochemical studies with nitroxide (**5**) yielded a reduction potential of -0.48 V, indicating a conceivable role in redox cycling *in vivo* with production of OS via ROS.<sup>17</sup> Only a small quantity of minor metabolites is required to generate large quantities of ROS since the operation is catalytic.

Brain microsomal reduction of norcocaine nitroxide generates SO.<sup>22</sup> Incubation of liver microsomes with either the nitroxide or the N-hydroxy derivative leads to lipid peroxidation, the degree of which is greater for the metabolites than for cocaine itself,<sup>23</sup> indicating the crucial role of the metabolites in toxicity. Redox cycling involving the metabolites is believed to take place, accompanied by formation of SO and lipid peroxy radicals.<sup>18</sup> Immunotoxicity in rats is promoted by N-oxidative metabolism, evidently via OS, accompanied by depletion in GSH.<sup>25</sup> Formaldehyde, an oxidative metabolite of **2** (Fig. 1)<sup>24</sup> is reported to produce ROS.<sup>14</sup>

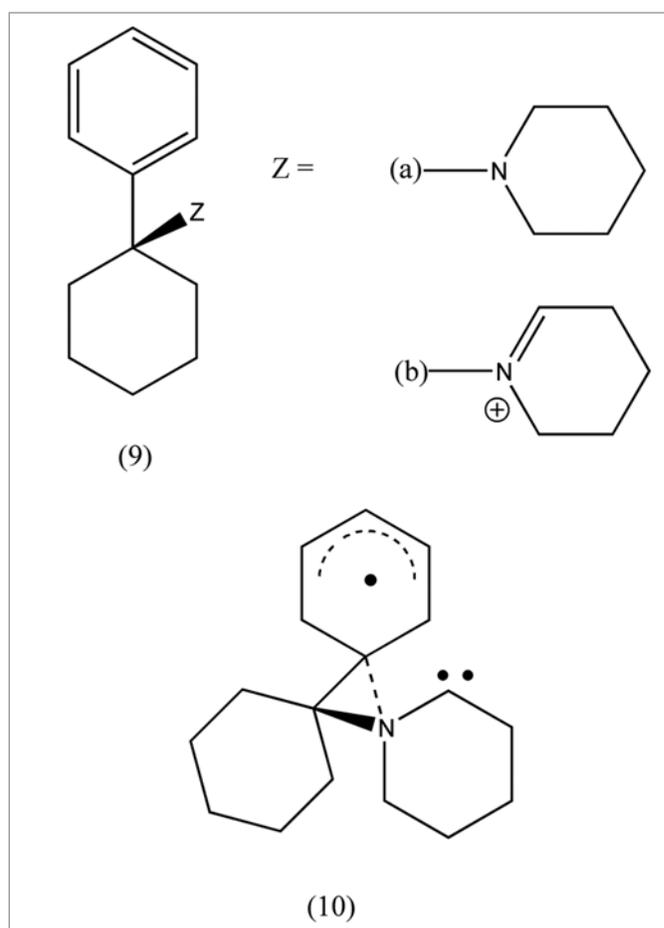
### 3,3'-Iminodipropionitrile Metabolism<sup>16</sup>

3,3'-Iminodipropionitrile (IDPN),  $\text{HN}(\text{CH}_2\text{CH}_2\text{CN})_2$ , an industrial intermediate, is used as an experimental neurotoxin.<sup>16</sup> Which might be related to (**2**) mechanistically. Administration produced a significant increase in malondialdehyde and decrease in vitamin E and glutathione (GSH), suggesting a role for ROS in toxicity.<sup>26</sup> Concurrent use of Se significantly inhibited IDPN-induced neurobehavioral changes in rats, and reduced ROS production, evidently through attenuation of toxicity by decreased lipid peroxidation.<sup>27</sup> Co-treatment with cysteamine protected rats against dyskinesia by IDPN.<sup>28</sup> Depletion of vitamin E and GSH through toxic action was alleviated by the thiolamine as AO. Similarly, adjuvant use of salicylate decreased abnormal neurobehavior and reversed GSH depletion, presumably by AO action of the phenol.<sup>29</sup>

Little is known about the action mechanism of IDPN. A clue is provided by one of several metabolites, namely the neurotoxic N-hydroxy derivative produced by flavin monooxygenase-mediated oxidation.<sup>30</sup> The data suggest that metabolism is necessary for certain neurotoxicities. There is similarity between IDPN and cocaine, both in structure and metabolism. By analogy with (**6**), the N-hydroxy form could operate in a redox cycle with the nitroxide radical, or nitrosonium could be involved. The ester and cyano substituents in the two toxins may play similar



**Figure 1.** Diazocilpine MK-801. This secondary-amine is addressed mainly in connection mechanism and physiological activity. Metabolism yields a hydroxylamine which may be associated with redox entities (Fig. 2), as in the case of cocaine. There is also similarity to 3,3'-iminodipropionitrile and phencyclidine. Mk-801 possesses a large number of physiological effects involving anesthesia, anticonvulsant, the CNS, memory, behavior, learning, fear and analgesia.



**Figure 2.** Phencyclidine and metabolites. Phencyclidine (PCP) (9a) has been extensively investigated as an abused drug. Mechanistic insight is gained from metabolic studies that show formation of iminium (9b). The electroreduction of 9b is facilitated by the aromatic nucleus despite lack of conjugation, indicating through space delocalization of the radical product. A computational report also supports this type of stabilization. MK-801 bears analogy by the presence of a beta-nitrogen possessing radical character from electroreduction of nitrosonium.

roles in intramolecular stabilization of the nitroxide radical and other reactive intermediates.

### Phencyclidine (PCP) Metabolism

MK-801 has been designated a PCP-type drug.<sup>31</sup> Results suggest that mode of action involves PCP receptors, not opioid types. Other results suggest that MK-801 induced hyperlocomotion may be mediated by NMDA receptor antagonism.<sup>32</sup> The data were similar to those for PCP. PCP-like drugs, such as MK-801, have many effects in common, including impact on learning and performance.<sup>33</sup> Similarity of the two drugs in various studies may indicate a similar mechanism entailing ET.

Theoretical studies on PCP provide useful insight.<sup>21</sup> It is well established that oxidative metabolism of PCP (**9a**) leads to the iminium species **9b**. Although **9b** is not directly conjugated with the aromatic nucleus, cyclic voltammetry studies indicated interactive stabilization of the reduced species. Recently, computational studies were performed on the energetics of electron uptake by **9b** with respect to conformation. In relation to the reduced species, thermodynamic preferences were found for conformations similar to that present in PCP bound to the active site. The through space delocalization is depicted in **9c**. The calculations suggest that a factor in the biological responses may be ET by the iminium metabolite.

### MK-801 Metabolism

A metabolic report provides important insight concerning the mechanism of MK-801 action.<sup>34</sup> With labeled drug, radioactivity was widely distributed among various tissues. Major metabolites were the N-hydroxy derivative, and the 2- and 8-hydroxyl analogs involving oxidation at carbon. The N-OH (hydroxylamine) product is the focus of our attention. Related literature (see above) demonstrates that subsequent oxidation products, such as nitroxide and nitrosonium ion can play an important mechanistic role.

### MK-801 ET Mechanisms

There are various means whereby the hydroxylamine-nitroxide redox coupling could operate. The main ones have been pointed out in the cocaine section. Other relevant reports exist. Results indicate that dismutation of superoxide is catalyzed by the oxoammonium/nitroxide redox couple for carbocyclic nitroxide derivatives.<sup>35</sup> Complexes were studied in which nitrosonium served as acceptor with aromatic donors.<sup>36,37</sup> The oxoammonium cation can be generated by reaction of nitroxide with various radicals.<sup>38</sup> Nitroxides might act as both anti- and pro-oxidants. Other nitrosonium ions and nitroxide can be generated in vivo and might serve in cell signaling and as cytotoxic agents.<sup>39</sup> Hence, there exists ample analogy for assigning a role for the hydroxylamine-nitroxide couple, together with associated species, in the bioactivity of MK-801. There is similarity to PCP in relation to nitrogen with radical character in the beta position to the aromatic ring. Alternatively, the phenolic metabolites formed at C2

and C8 may conceivably play a role. Phenols are well-known metabolic precursors of ET quinones.

### Receptors

MK-801 binds at two sites on the NMDA receptor-ion channel complex, which is a glutamate (Glu) receptor.<sup>40</sup> Glu is a main excitatory neurotransmitter in the brain. The drug attaches to the ion channel at the PCP binding site of the receptor, requiring depolarization of the neuron. Receptor blockage by MK-801 occurs in a voltage-dependent manner. Our proposed ET mechanism with accompanying electrical effects is in keeping with the receptor phenomena.

In a recent publication, the sub-unit mechanisms and proton sensitivity of NMDA receptor channel block were discussed.<sup>41</sup> The transient ischemia during occlusive stroke triggers changes in the nature of the extracellular milieu, including strong acidification of the ischemic core with more modest acidification of penumbral regions. NMDA receptors are inhibited by protons at pH 6.9–7.3, suggesting that even modest acidification could reduce or delay the contribution of NMDA receptors to neuronal death until pH gradients surrounding the ischemic insult dissipate. Mutagenesis studies of NMDA receptor subunits suggest that residues in the linker regions connect the agonist binding domain to the transmembrane pore-forming elements proton-sensitive gating. The authors show the binding capabilities of several proton-dependent channel blockers, kinetic modeling and single channel experiments using acidic extracellular pH, which reduce receptor open probability, increases the association rate of optical isomer (-)MK-801, but not isomer (+)MK-801.

Iron is thought to play a critical role in pathogenesis of neurodegenerative disorders, as Parkinson's and Alzheimer's diseases, by the generation of oxygen-free radicals in association with oxidative stress. Ferrous chloride markedly inhibited, in a concentration dependent manner, dizolciline binding to an open ion channel associated with NMDA receptor in rat brain synaptic membranes. Addition of an NMDA agonist, such as, spermidine, attenuated the inhibition of MK-801 binding. The results suggest that ferrous ions may interfere with opening processes of the native NMDA channel through molecular mechanisms peculiar to neuronal development in a manner associated with the polyamine recognition domain.<sup>42</sup>

### Oxidative Stress

A study with MK-801 showed that induced neurotoxicity involved OS in the prefrontal cortex of rats.<sup>43</sup> A protective effect was shown by caffeic acid phenethyl ester (CAPE) an inhibitor of ROS generation.<sup>44</sup> Induction of schizophrenia by MK-801 resulted in significant OS, involving increases in malondialdehyde and protein carbonyl levels.<sup>45</sup> Administration of CAPE reduced the detrimental histopathological changes. The drug influences lipid metabolism and the intensity of lipid peroxidation.<sup>45</sup> MK-801-induced neurotoxicity causes OS in the prefrontal cortex of rats.<sup>43</sup>

## Anesthesia

Results indicate that blockage of the central NMDA receptor may contribute to the production of anesthesia.<sup>46</sup> The ability of the receptor antagonists to increase the potency of general anesthetics paralleled their potency as NMDA antagonists and their affinity for the PCP receptor site of the NMDA receptor-ionophore complex: MK-801 > PCP > ketamine. MK-801 is not used clinically as an anesthetic due to development of brain lesions.

The discriminative stimulus effect of MK-801 in ketamine-trained rats was investigated.<sup>47</sup> The results indicate that both drugs may share a common mechanism of action, which is related to the phencyclidine recognition site in the brain.

A recent report lends credence to the ET approach in anesthetic action involving propofol.<sup>48</sup> Four years ago, a novel unifying hypothesis was advanced for addiction and toxicity by abused drugs involving ET.<sup>10</sup> One of the principal ET agents is the quinone group which is often generated metabolically. Appreciable numbers of abused drugs appear to function by the quinone route, including amphetamine, methamphetamine, ecstasy, morphine, heroin, phenobarbital and aspirin. Recently, two members were added to the quinone category, namely, mescaline<sup>49</sup> and psilocybin.<sup>50</sup>

Inflated rates of opioid addiction among anesthesiologists may be caused by chronic exposure to low doses of anesthetic agents, such as propofol (2,6-diisopropyl phenol), in the operating room.<sup>51</sup> Such second-hand exposure results in neuro sensitization of the reinforcing effects of the anesthetic, making later addiction more likely. Second hand exposure could occur by inhalation or skin contact. Other factors may be involved.

Various reports on metabolism of propofol provide insight concerning action mechanism. Analysis of products from oxidative metabolism revealed the presence of 2,6-diisopropyl-1,4-quinone,<sup>52</sup> in addition to the quinone dimer (diphenoquinone).<sup>53</sup> More specifically, it is reasonable to focus on involvement of ET processes and electrical fields. The radical anion semiquinone provides molecular electrostatic potential. Since ET by quinone is often associated with generation of ROS, these radicals, at low levels, may play a role. At high concentrations, toxicity could result.<sup>10</sup> There has been scant attention paid to action mode at the molecular level. These results provide additional support for the hypothesis based on ET by addictive agents.

## Anticonvulsants

MK-801 is a potent anticonvulsant which displays high affinity for binding sites in rat brain membranes, particularly in the hippocampus.<sup>54</sup> None of the major neurotransmitters was active at these sites. The only competitive substances were those that block the responses of excitatory amino acids mediated by NMDA receptors, including phencyclidine and ketamine. These findings provide a clue to the action mechanism.

Also, a 1992 review advanced the proposal that ET may be a possible mode of action for anticonvulsants.<sup>55</sup> The conjugated iminium functionality is a common one among the active drugs.

The resulting flow of electrons from ET would generate electrical fields, thereby affecting ion movement in membrane channels and nerve synapses.

## Brain Electrochemistry

A study of brain field potentials revealed a particular pattern of charges which was very stable over time.<sup>56</sup> Higher doses of MK-801 produced a continuous change from power decreases to increases, accompanied by strong behavioral effects involving impaired locomotor control. Changes in the frequency content of the field potentials occurred over time. The present authors believe that the electrical effects may be related to ET properties of the MK-801 metabolites.

## Other Brain Effects

MK-801 failed to reduce infarct size in animals whose body temperature rose during ischemia. In contrast, the drug markedly reduced infarct volume in temperature controlled animals. The results suggest that amelioration of focal cerebral ischemia cannot be expected if body and brain temperature is allowed to rise above normal.<sup>57</sup>

Gao et al. showed phencyclidine and MK-801 exert time-dependent effects on the expression of immediate early genes in rat brain.<sup>58</sup> The mRNA expression pattern for four different immediate early genes was examined dynamically in rat brain after administration of PCP or MK-801. Following each treatment, the expression of mRNA changed. The authors suggest functional consequences of PCP- or MK-801-induced reduction in NMDA-sensitive glutamate transmission may be relevant to an understanding of animal NMDA pharmacology and/or to clinical psychotomimetic side effects of ant glutamatergic treatments.

Bilateral injection of dizocilpine into the anterior thalamus of rat brain induced HSP70 protein formation in pyramidal neurons in deep layer III retrosplenial cortex. This bilateral blockade of NMDA receptors in the anterior thalamus by MK-801 injures neurons in retrosplenial cortex.<sup>59</sup>

Delta sleep-inducing peptide has been shown to increase the resistance of rats to stress. Increase in the expression of the early c-fos in the paraventricular nucleus of the hypothalamus is regarded as the primary response of animals in conditions of emotional stress. Injection of the peptide leads to decrease in stress-induced c-fos expression in the paraventricular nucleus of the hypothalamus. Exposure to MK-801 blocks the effects of delta sleep-inducing peptide-induced suppression of c-fos gene expression.<sup>60</sup>

## CNS Effects: Neurotoxicity and Neuroprotection by MK-801<sup>8</sup>

NMDA antagonists, such as, MK-801, disrupt sensorimotor gating in rats, suggesting that the effects may provide a model of such deficits exhibited in schizophrenia.<sup>61</sup> MK-801, a non-competitive NMDA receptor antagonist, is a well known neuroprotectant in models of stroke, trauma, Parkinsonism and

organophosphate-induced seizures. Despite this, MK-801, like other phencyclidine receptor ligands, such as phencyclidine, ketamine or tiletamine, induces psychotic behavior and neuronal degeneration. MK-801 exposure caused neuronal degeneration in rat axon terminals, microglia, retrosplinal cortex, neurons in the pyriform, and entorhinal cortices, in amygdala in tenia tecti, and in the temporal dentate gyrus.<sup>62</sup>

MK-801 affected the nervous system of male and female rats differently.<sup>63</sup> Female rats indicated higher sensitivity to MK-801 neurotoxicity; Authors suggest the possible involvement of 17 $\beta$ -estradiol in the sex differences of the sensitivity. The female rats also showed increased glial fibrillary acidic protein when treated with MK-801 vs. the male rats.

Non-competitive NMDA antagonist MK-801 and phencyclidine increase glucose metabolism in many brain areas and induce cytoplasmic vacuoles, heat shock protein and necrotic cell death in neurons of the rodent posterior cingulate and retrosplinal cortex. Administration of radical scavengers (dimethyl sulfoxide and  $\alpha$ -tocopherol), produced marked attenuation of MK-801-induced neuronal necrosis. This supports the hypothesis that OS plays a role in MK-801-induced neuronal necrosis since pathological changes are attenuated by several AOs.<sup>64</sup>

Glutamate, the most widely used excitatory amino acid transmitter in the brain, stimulates ionotropic and metabotropic receptors. There is an increased release of glutamate after cerebral ischemia or hypoxia which cause overstimulation of its receptors, leading to an increase in the cellular Ca<sup>2+</sup> concentration. Elevation of Ca<sup>2+</sup> is assumed to set various pathological processes into motion which degenerate neurons by activating proteases, lipases, endonucleases and nitric oxide synthases and by promoting the formation of free oxygen radicals. MK-801-treated cultures of rat hippocampal neurons showed a neuroprotective effect.<sup>65</sup> The influence of MK-801 on release of inhibitory amino acids in the field of neuroprotection against ischemic injury was explored. The protection against brain damage induced by ischemia, at least partly, is related to inhibition of calcium influx and, more significantly, blockage of excitatory amino acid release from ischemic synaptosomes.<sup>66</sup> In a related study, paraquat or xanthine oxidase was shown to activate the NMDA receptor and the resultant excitatory amino acid glutamate leads to excitotoxicity. Dizocilpine attenuates this oxidant injury, acting as an AO.<sup>67</sup>

In vitro studies have demonstrated that NMDA receptor activation rescues cerebellar granule neurons from apoptotic death. Mechanism involves MK-801 inhibiting the caspase activation.<sup>68</sup> Nitroxyl anion (NO<sup>-</sup>), and/or its conjugate acid, HNO, may be formed in the cellular milieu by several routes under both physiological and pathophysiological conditions. Reactive nitrogen oxide species can contribute significantly to cerebral ischemic injury. A study using Angeli's salt, a spontaneous HNO/NO<sup>-</sup> generating compound, showed time- and concentration-dependent increase in neural cell death. Addition of glutamate receptor antagonist MK-801 to the culture reduced the toxicity, acting as an antioxidant.<sup>69</sup> In a related study, low doses of MK-801 were shown to protect iron-induced oxidative changes in a rat model of focal epilepsy, suggesting MK-801

acts as an antioxidant against both free radicals and excitatory amino acids in epilepsy.<sup>70</sup>

L-2-Chloropropionic acid, when administered orally to rats, produces selective necrosis to the granule cell layer of the rat cerebellum, which is delayed in onset, after exposure. Administering MK-801 afforded partial protection against the toxicity.<sup>71</sup>

The effect of pro-inflammatory cytokine interleukin IL-1 $\beta$  on the hippocampal slices from neonatal Sprague Dawley rats was examined, and neuroprotective action by MK-801 and vitamin-E analog trilox was shown. The neuroprotective effects suggest that free radicals and NMDA receptor-mediated processes are involved in IL-1 $\beta$  induced neurodegeneration.<sup>72</sup>

Organophosphates and carbamate inhibitors acetylcholinesterase produce seizures and lethality in mammals. MK-801 blocked these seizures. Results suggest that NMDA receptors seem critical to such seizures.<sup>73</sup>

### Motor Activity, Learning and Memory

Glutamate transmission plays an important role in many behavioral systems, including motor activity, learning, and memory. The noncompetitive NMDA receptor antagonist MK-801 has been shown to increase motor activity and to impair learning and memory in a variety of tasks in rats, mice and other species.

Many agents, e.g., MK-801, that antagonize the NMDA receptor-channel complex also cause disturbances of motor coordination.<sup>74</sup> The effects of MK-801 upon motor activity and memory of rats were assessed in behavior testing. The results indicated MK-801 can produce profound effects upon motor activity and memory, and that these two effects can be dissociated.<sup>75</sup>

The long-lasting effects of a single high dose treatment with MK-801 on water maze performance of rats was reported. The drug-treated rats learned to find the escape platform at a slower rate than control animals and showed increased thigmotaxis during acquisition of the task.<sup>76</sup> A study demonstrated that MK-801 impairs working memory of conscious monkeys. In addition, acute and chronic MK-801 produces different effects on receptor D1, D2 and generally lowered glutamate and dopamine levels in prefrontal cortex.<sup>77</sup> The effects of MK-801 on learning ability in non-human primates were investigated. MK-801 impaired acquisition of visuo-spatial tasks requiring spatial responses to colored objects, and perceptually difficult visual discrimination tasks.<sup>78</sup>

### MK-801 Induced Behavior

MK-801 in rats induced characteristic behavioral syndrome with ataxia, stereotypies and hyperlocomotion. Part of the behavioral syndrome is thought to be related to interactions between glutamatergic and dopaminergic neurotransmission, suggesting serotonin involvement.<sup>79</sup> In a related study involving psychotic-like behavior induced by MK-801 and serotonin receptors, the authors conclude that there is an interaction between NMDA and serotonin receptors.<sup>80</sup>

With zebrafish as a neurobehavioral model, MK-801 increases circling behavior, alters swimming activity, and impairs place preference.<sup>81</sup> Data indicate that systemic administration of a

relatively small dosage of MK-801 facilitates performance when reward is small. Facilitation may be due to the reinforcement of mechanisms that work in opposition to response bias.<sup>82</sup>

### **Circadian Behavior and Sleep Induction**

The NMDA receptor antagonist MK-801 blocks the phase shifting effects of light on the circadian rhythm in hamsters.<sup>83</sup> A dose-dependent blockade of both light-induced phase advances and delays occurred. The data indicated an important role for excitatory amino acid receptor in transmission of light information from the retina to the circadian system.

A commonly used sleep inducer is zolpidem (Ambien).<sup>84</sup> A proposed action mechanism comprises protonation to a conjugated pyridinium (iminium) structure which may function as an ET agent. Electrochemical phenomena may be responsible for sleep induction and adverse side effects.

### **Abused Drugs**

Upon repeated exposure to drugs of abuse, the gradual development of tolerance, dependence and sensitization is thought to play a crucial role in the psychopathology of drug addiction.<sup>85</sup> In recent years, NMDA receptor antagonist MK-801 has been widely used to investigate the involvement of NMDA receptors in drug-induced neuroadaptations. Dizocilpine shares stimulus properties with phencyclidine and, to lesser extent, with ethanol. Dizocilpine was found to potentiate the reinforcing properties of morphine and cocaine in models. Regarding the cerebral sites where dizocilpine might exert its reinforcing effects, several areas were designated as likely candidates. However, dizocilpine and morphine were found to dramatically enhance lethality. Dizocilpine was shown to prevent, as well as enhance, the development of drug-induced behavioral effects, and appears to induce sensitization to its own behavioral effects, as well as cross-sensitization to drugs of abuse.

Studies were carried out on rats implanted with morphine.<sup>86,87</sup> The naloxane-precipitated abstinence syndrome in rats exposed to MK-801 was more intense than controls, whereas the abstinence syndrome in rats that received MK-801 before naloxane injection was less intense. The intensification is attributed to increase in upregulation and supersensitivity of NMDA receptors caused by morphine. The attenuation is explained based on blockage by MK-801 of NMDA receptors. Related studies are reported for morphine and MK-801. The present authors believe ET events may be involved in line with the recent unifying hypothesis for abused drugs.<sup>10</sup>

In a related study, results indicate that MK801 not only blocks the development of morphine-induced conditioned place preference, but it is also able to block the expression of a conditioned response that has been acquired.<sup>88</sup>

Glutamate receptor activation participates in mediation of neurotoxic effects in the striatum induced by the psychomotor stimulant amphetamine. MK-801 inhibits amphetamine-induced formation of nitric oxide, lipid peroxidation and

amphetamine-induced release of amino acids and acetylcholine in rat brain. Part of the effect reflects action as an AO.<sup>89</sup>

Methamphetamine causes long-term toxicity to dopamine nerve endings of the striatum. In vivo experiments show that MK-801 ability to protect against methamphetamine neurotoxicity is related to their common property as blockers of microglial activation.<sup>90</sup>

Another drug in this category is mescaline (peyote) whose mode of action has been discussed recently.<sup>49</sup> The proposed mechanism entails demethylation to a catechol moiety which then has the potential of redox cycling with an ET o-quinone. Electrochemical effects may be involved in the hallucinogenic and other effects.

### **MK-801/NMDA Receptor and Bioactivity**

The prior sections illustrate the variety of this drug in the biological realm. The following portion provides recent literature from 2008–2009 dealing with memory, behavior, learning, fear, pain control and anesthesia.

Various literature reports address the role of MK-801 in memory. Inhibition of NMDA Glu receptors during food aversion conditioning reactivation initiated disruption of long-term memory.<sup>91</sup> Injection of MK-801 produced a decrease in the number of conditioned food aversions. The long-term memory reactivation disruption induced two stages of amnesia development. The NMDA Glu receptor is implicated in memory formation and consolidation.<sup>92</sup> Administration of MK-801 immediately after training impaired inhibitory avoidance performance, suggesting induction of state-dependent recall. NMDA receptor antagonists induce amnesia.<sup>93</sup> Data revealed that MK-801 produced anterograde and retrograde amnesia. Pharmacological disruption of reconsolidation of alcohol-associated memories can be achieved by use of NMDA antagonists, such as MK-801.<sup>94</sup> This may be a therapeutic strategy for prevention of relapse in alcohol addiction. Studies were made of MK-801 involvement in working memory processing in the medial prefrontal cortex.<sup>95</sup>

MK-801 has been employed in behavioral studies. Deficits in behavior were noted following treatment by NMDA antagonists, such as MK-801. More specifically, there was increased anxiety-like behavior.<sup>96</sup> The effects of MK-801 treatment on rat behavior were observed after neonatal lesions of the entorhinal cortex.<sup>97</sup> The combined treatment may serve to model certain aspects of psychiatric behavior. A genetically-inbred mouse strain shows heightened sensitivity to the ability of MK-801 to raise the threshold voltage necessary to precipitate tonic hindlimb extension and elicit irregular episodes of intense jumping behavior.<sup>98</sup> The heightened behavioral sensitivity to MK-801 does not appear to result from alterations of expression of the NMDA receptor protein subunits. Behavioral flexibility refers to the ability to modify ongoing behavior in response to changing goals or environmental contingencies.<sup>99</sup> Administration of MK-801 significantly impaired task performance. The amygdala appears to be a primary locus in mediating the effects of drug stimuli on subsequent drug-seeking behavior.<sup>100</sup> The NMDA subtype of the Glu receptor within

the amygdala is important for consolidation of associations between environmental conditioned stimuli and the effects of additive drugs. Systemic antagonism of NMDA receptors with MK-801 before memory reactivation reduced acquired drug-seeking behavior that depends on drug-associated cues acting as conditioned reinforcers. Such drugs may be useful in treatment of relapse prevention in drug addiction.

Effect on learning has been examined for MK-801. Food aversion conditioning consolidation was investigated with various substances in snails.<sup>101</sup> The conditioning was absent after molecular mechanisms evoked disruption of long-term memory consolidation during learning. Treatment of mice with MK-801 induced learning impairment, accompanied by inhibition of NMDA-stimulated phosphorylation.<sup>102</sup> Ginsenoside Rg 1 improves spatial learning capacity impaired by morphine, and restores the morphine-inhibited long-term potentiation.<sup>103</sup> This effect is NMDA receptor dependent, as evidenced by experiments with MK-801. Systemic administration of the drug impairs reversal learning in rats.<sup>104</sup> The study entailed spatial discrimination. Administration of MK-801 before exposure to ethanol significantly inhibited ethanol state-dependent learning.<sup>105</sup> Dorsal hippocampal NMDA receptors are involved in mediating the learning process.

The influence of MK-801 on fear has been investigated. A study addressed whether Ro-64-6198 impairs acquisition of fear conditioning through glutamatergic mechanisms.<sup>106</sup> Administration of Ro-64-6198 and MK-801, either separately or concomitantly, reduced the facilitating effects of context exposure. The findings demonstrate the existence of functional antagonism between NMDA and nociceptin opioid peptide receptors that predominantly contributes to modulation of conditional fear learning that involves spatial-processing demands. The role of conditioned stimulus familiarity in determining the effects of MK-801 on fear extinction was shown to be an important factor.<sup>107</sup> The drug impaired extinction learning about novel stimuli,

but spared extinction learning about familiar stimuli. Long-term fear memory can be extinguished by disruption of reconsolidation of specific memories associated with the fear response.<sup>108</sup> The effects of MK-801 on memory reconsolidation were studied. Neurotransmitters that are important for extinction of conditioned fear in adult rats are not important for extinction in young rats.<sup>109</sup> Pre-extinction injection of MK-801 has no effect on extinction in young rats, whereas it impairs long-term extinction in older rats.

In relation to pain control, the mechanism of orthodontic pain is poorly understood.<sup>110</sup> By use of a behavioral model, application of both systemic and peripheral MK-801 and morphine exerted an analgesic effect. Face-grooming behavior is a reliable measure for tooth pain in rats. Cyclooxygenase-2 (COX-2) is upregulated and plays an important role in pain and hyperalgesia induced by nociceptive stimulation.<sup>111</sup> Activation of the spinal NMDA receptor might contribute to the upregulation of COX-2 spinal expression. Results show that injection of MK-801 suppressed the upregulation of the COX-2 expression and characteristic pain behavior responses.

In a study of anesthetics, classical ones of the gamma-aminobutyric acid (GABA) type A receptor-enhancing class, e.g., phenobarbital and chloral hydrate, produce analgesia and unconsciousness (sedation).<sup>112</sup> Dissociative anesthetics that antagonize the NMDA receptor, e.g., MK-801, ketamine and PCP, produce analgesia, but do not induce complete loss of consciousness. From a mechanistic study, the authors hypothesize that neural substrates of sleep-wake behavior are engaged by low-dose sedative anesthetics, and that the mesopontine descending noradrenergic cell groups contribute to the analgesic effects of both NMDA receptor antagonists and GABA (A) receptor-enhancing anesthetics.

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