Critical Review

Neuropsychotoxic and Neuroprotective Potentials of Dextromethorphan and Its Analogs

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Abstract. Dextromethorphan (3-methoxy-17-methylmorphinan) has complex pharmacologic effects on the central nervous system. Although some of these effects are neuropsychotoxic, this review focuses on the neuroprotective effects of dextromethorphan and its analogs. Some of these analogs, particularly dimemorfan (3-methyl-17-methylmorphinan) and 3-hydroxymorphinan, have promising neuroprotective properties with negligible neuropsychotoxic effects. Their neuroprotective effects, the mechanisms underlying these effects, and their therapeutic potential for the treatment of diverse neurodegenerative disorders are discussed.

Keywords: dextromethorphan, dimemorfan, 3-hydroxymorphinan, neuroprotection, neuropsychotoxicity, neurodegenerative disorder

1. Introduction

Dextromethorphan (DM, 3-methoxy-17-methylmorphinan), a common ingredient in more than 125 commercial cough and cold remedies, is a dextrorotatory optical isomer of levomethorphan, a typical morphine-like opioid that is the codeine analog of the morphinan derivative levorphanol. Patented by Hoffmann–La Roche in 1954 as an antitussive agent, DM has strong safety and efficacy profiles with no sedative or addictive properties at recommended antitussive doses (1). As an antitussive, DM is superior to opioids used at antitussive doses in that it lacks their gastrointestinal side effects, such as constipation, and causes less depression of the central nervous system.

In the past decade, investigators have documented that DM is an antagonist of \(N\)-methyl D-aspartate (NMDA) receptors and a neuroprotective agent. However, its neuroprotective effect is only seen at a dosage much higher that that used for cough suppression. The psychotropic effects that can result from the clinical use of high doses of DM (2, 3) and the fact that DM has been recognized as the object of drug-seeking behavior in several countries (4, 5) have hampered its pharmacologic development as a useful neuroprotective agent. In this review, we will discuss the complex behavioral effects of DM; demonstrate its neuroprotective effects; and discuss its analogs, such as dimemorfan (DF, 3-methyl-17-methylmorphinan) and 3-hydroxymorphinan (3-HM), which have neuroprotective effects with improved safety profiles. The chemical structures of DM and its analogs are shown in Fig. 1.

2. Metabolism of DM

DM is rapidly absorbed from the gastrointestinal tract into the bloodstream. At oral therapeutic doses, it begins to act within 15 – 30 min of administration, reaching its peak serum level within 2 – 2.5 h (6, 7). It crosses the blood–brain barrier with a cerebral spinal fluid/plasma
ratio of 33% – 80% (6) and a duration of action of 5 – 6 h (7).

DM is metabolized primarily through O-demethylation, which produces dextrorphan (DX), and also to some extent through N-demethylation, which yields 3-methoxymorphinan. Both metabolites are further demethylated to 3-hydroxymorphinan (3-HM) (Fig. 2). Urinary recovery studies in humans and rats have shown that DX and 3-HM are excreted largely (> 95%) as glucuronide conjugates (8). The pharmacology of 3-methoxymorphinan is not significant, and it does not have major behavioral side effects. However, as discussed later in this review, we have observed that 3-HM offers anti-parkinsonian effects with absolute safety.

DX, the major metabolite of DM, has neuroprotective potential (9). Its affinity for the NMDA Ca\(^{2+}\)-channel complex is lower than that of DM, but its affinity for the phencyclidine [PCP, 1-(1-phenylcyclohexyl)piperidine] binding site on the complex is higher than that of DM; DX binding to the NMDA-receptor complex produces PCP-like discriminative stimulus effects (10). The extent of the metabolic conversion of DM to DX is highly dependent on the route of administration (8); intraperitoneal (i.p.) administration of DM, whereby it is absorbed into the hepatic portal circulation, greatly favors production of DX, while subcutaneous (s.c.) administration is less favorable for DX production (8).

3. DM-induced neuropsychotoxicity

3.1. Behavioral side effects

Results of animal studies have suggested that most symptoms observed in abusers of DM are caused by DX, which binds to the same central nervous system receptors
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as PCP. In mice, long-term oral administration of a neuroprotective dose of DM produces behavioral suppression followed by behavioral tolerance, and prenatal exposure to DM produces hyperlocomotor activity in the offspring. When these offspring receive additional DM, they demonstrate marked behavioral depression (11). Mice exposed to long-term oral DM treatment exhibit impaired B-cell function and natural killer-cell cytotoxicity, similar to the immunosuppressive effects of PCP (12).

Ample evidence indicates that DM has effects of its own that are independent of its conversion to DX. Holtzman (13) has reported that DM (30 mg/kg, s.c.) has PCP-like discriminative effects that are independent of its conversion to DX; these effects are most easily appreciated in vitro, where metabolism is not an important issue. Interestingly, DM (13) and DX (10) are completely interchangeable for PCP in rats trained to distinguish PCP from saline, and DM also substitutes for DX in pigeons trained to discriminate DX from saline (14). Therefore, the route of administration is an important determinant in the deposition of DM and its metabolites, as well as in its behavioral effects.

DM alters the behavioral response to several drugs of abuse, including morphine, methamphetamine, and cocaine. DM (25 mg/kg, i.p.) reduces methamphetamine self-administration in rats but does not affect the response to a food reward (15). In addition, the co-administration of DM (20 mg/kg, i.p.) with methamphetamine (2 mg/kg, i.p.) attenuates methamphetamine-induced psychological dependence [conditioned place preference (CPP)] and behavioral sensitization (16). Pretreatment with DM (20 mg/kg, s.c.) potentiates the effects of acute morphine exposure, while it attenuates the effects of chronic morphine exposure on dopamine release in the nucleus accumbens (15).

Pulvirenti et al. (17) demonstrated that DM (25 mg/kg, i.p.) reduces the self-administration of cocaine at various doses (0.12, 0.25, and 0.5 mg/kg per 2-h infusion) in rats, consistent with other findings (18). However, Kim et al. (18) reported that oral DM (40 mg/kg) increases the rate of reinforced responses to lower doses of cocaine (0.06 and 0.03 mg/kg per infusion). Therefore, DM shifts the dose–response curve for cocaine self-administration to the left, suggesting a sensitized response to the reinforcing effects of cocaine. Consistent with this interpretation, Jhoo et al. (19) reported that DM (i.p.) has a biphasic effect on cocaine-induced psychological dependence, as evaluated by CPP. DM decreases CPP induced by high doses of cocaine and increases CPP induced by low doses (19). Furthermore, Kim et al. (20) found that DM exerts biphasic effects on cocaine-induced locomotor stimulation in mice and that the locomotor activities parallel Fos-related antigen immunoreactivity in the striatal complex. Therefore, the cocaine-induced behavioral response is influenced by pre-exposure to DM, although the responses might also be affected by the route, period, or interval of administration or by the animal model.

3.2. Neurotoxicity

A single exposure to a non-competitive NMDA-receptor antagonist, such as MK-801, PCP, or ketamine, has been reported to cause pathological damage in the posterior cingulate cortex and retrosplenial cortex of rat brain (21). These chemicals can induce heat shock protein HSP-70, which may play a role in cellular repair and/or protective mechanisms in the same regions (22). Hashimoto et al. (23) found that the induction of HSP-70 protein in the posterior cingulate and retrosplenial cortex of the rat brain was maximal at a DM dose of 75 mg/kg (i.p.). In contrast, Carliss et al. (24) found that high-dose oral DM did not produce the neuropathologic changes caused by other NMDA-receptor antagonists, suggesting that the disposition of DM and its metabolites in rat brain depends on the route of administration. However, our preliminary findings (data not shown) indicate that an understanding of the precise neuropathologic mechanisms mediated by high-dose DM will require more

Fig. 2. Metabolic pathway of DM. CYP=cytochrome P450, DM=dextromethorphan, 3-MM=3-methoxymorphinan, DX=dextrorphan, 3-HM=3-hydroxymorphinan.
3.3. Cognitive dysfunction

Substantial evidence indicates that NMDA receptors play a significant role in the synaptic plasticity (25) believed to form the basis for certain commonly studied learning and memory processes involving the hippocampus. Some forms of long-term potentiation, a putative physiological process underlying learning and memory, have been shown to be NMDA receptor–dependent (26). Furthermore, many studies indicate that NMDA-receptor antagonists that interfere with long-term potentiation also disrupt performance on learning tasks, particularly those involving spatial memory (27). Because NMDA receptors are involved in both synaptic plasticity and neurodegenerative processes, potential anticonvulsant/neuroprotective drugs targeting this receptor must be evaluated in terms of their possible interference with normal learning and memory processes.

DM has been suggested to prevent the induction of long-term potentiation in vivo (28). In addition, investigators have demonstrated that DM (29) and DX (30) impair passive avoidance in rats. Similarly, DM has been reported to impair spatial learning in the Morris water maze in a dose-dependent manner (31), consistent with the water-maze effects of other NMDA-receptor antagonists (e.g., MK-801 and AP-5) reported by other investigators (26). On the other hand, the memory impairment caused by DX is more pronounced than that of DM (32), and the prolonged use of DM produces cognitive deterioration in humans (33).

4. Neuroprotective effects of DM

4.1. Anticonvulsant effects

DM has been reported to suppress seizures induced by maximal electroshock (34, 35), NMDA (36, 37), amygdala kindling (38, 39), kainic acid (40, 41), BAY k-8644 (42, 43), and trimethylylthyl (44). DX (the dextrorotatory form of levorphanol) has similarly been reported to suppress seizures induced by maximal electroshock (34), NMDA (36), and BAY k-8644 (42, 43). Most studies have found that DX is several times more potent than DM as an anticonvulsant, suggesting that the metabolite formed in vivo significantly contributes to the anticonvulsant activity of the parent drug (45). However, some data suggest that the conversion of DM to DX is not necessarily required for DM to produce its effects in vivo (46). Both DM and DX show high binding affinities for 1-type receptors, but DM binds 2–5 times more tightly than DX (47), despite the greater anticonvulsant potency of DX. Thus, the mechanisms underlying the anticonvulsant action of DM and DX remain unclear at this point.

In addition to interacting with receptors, DM also weakly inhibits NMDA receptor–mediated responses (48, 49), which seems to be mediated by binding to a non-competitive antagonist site of the NMDA-receptor cation channel (50). Compared with DM, DX is several times more potent as an NMDA-receptor antagonist (51), which is consistent with its higher anticonvulsant effects in vivo.

Noting that DM decreases seizure intensity in fully kindled rats, Feeser et al. (38) have endorsed clinical testing of DM as an anticonvulsant drug, but Takazawa et al. (39) have demonstrated that DM has a narrow therapeutic window as an anticonvulsant for kindled seizures. Furthermore, the active metabolite DX has been reported to be ineffective against amygdala-kindled seizures (52). Takazawa et al. (39) have also reported that treatment of animals with DM (30–50 mg/kg body weight) leads to hindlimb ataxia and sedation in a dose-dependent manner, although without resting electroencephalographic changes. The proconvulsant activity of DM may depend on the experimental model, as echervarria et al. (53) have shown in rats that DM has anticonvulsant effects in the maximal electroshock test and proconvulsant effects in the flurothyl test.

Leander (37) has argued that antitussives have an anticonvulsant action separate from their PCP-like blockade of NMDA receptors. In this respect, a previous report that DM and DX, but not MK-801, can effectively block voltage-gated inward calcium and sodium currents in neurons (54) is of considerable interest, as these effects could explain why antitussives, but not more selective NMDA-receptor antagonists such as MK-801, act as anticonvulsants in kindling models. Indeed, it has been suggested that the primary mechanism of action of DM is simply a blockade of certain ion channels (9). In addition to its direct effects on voltage-gated cation channels, DM might also have anticonvulsant effects resulting from its binding to receptors (9, 34, 44, 47, 55), although the role of receptors in anticonvulsant drug actions remains to be determined. Both anticonvulsant and proconvulsant effects have been reported for 1-site ligands (9).

Radiolabeled DM binds to high-affinity sites in the brain; these sites are strikingly similar in their binding characteristics and regional distribution to 1-binding sites and are modulated by the antiepileptic drug phenytoin (9, 45). Indeed, at least one of the high-affinity DM-binding sites is identical to the 1 site (56). Autoradiographic studies have shown that high-affinity DM-binding sites are distinct from the high-affinity DX-binding site that is associated with the activated state of the NMDA-receptor cation channel complex (57). DX has a low affinity for
DM-binding sites in the brain but is eight times more potent than DM as a [3H]DX-binding inhibitor (57), consistent with its higher potency as an NMDA-receptor antagonist. In addition to σ1-site ligands, a variety of calcium channel antagonists compete for the σ1 sites that presumably act as high-affinity DM-binding sites (9), raising the possibility of an association between DM and voltage-gated ion channels.

The fact that DM and DX exert biphasic effects on neural excitation, as exemplified by the observations of both anti- and proconvulsant effects in the same convulsive animals, suggests that these drugs will have only a narrow therapeutic window in epileptic patients, if they have any effect at all. Earlier studies have suggested that epileptogenesis renders the brain more susceptible to the PCP-like adverse effects of NMDA-receptor antagonists (58). Many findings are not compatible with the idea that DM is just a prodrug for DX. Rather, they strongly suggest that the parent drug is primarily responsible for the anticonvulsant effects observed in vivo, at least in kindling and kainic acid models.

Previous studies have demonstrated that DM prevents seizures, mortality, and hippocampal cell loss in a dose-dependent manner (34, 40, 44, 55). One interpretation for the neuroprotective effects of DM vis-à-vis its anticonvulsant effect is that it reduces the excitotoxic effect of glutamate on neurons by inhibiting NMDA receptors (59). DM has also been shown to attenuate kainic acid–induced increases in activator protein-1 (AP-1) binding activity and c-Jun/Fos–related antigen expression in the hippocampus, collectively suggesting that DM is an effective antagonist of kainic acid and a powerful protectant for convulsants (40, 49).

### 4.2. Effects on cerebral ischemia

DM treatment has been shown to protect the brain against infarction and the related pathophysiological and functional consequences of ischemic injury in several in vivo ischemia models (60). In addition, several in vitro (61) and in vivo (62) studies have confirmed the neuroprotective actions of DM and have offered critical insights into its possible cellular mechanism of action. In particular, comprehensive studies undertaken with a rodent focal ischemia/reperfusion injury model have shown that DM has a potent ability to decrease the volume of cerebral infarction and to improve functional recovery as post-injury therapy (62).

DM attenuates the loss of vulnerable neurons in the CA1 region of the hippocampus in global ischemia models (63) and decreases cerebral infarct size in areas of severe neocortical damage after ischemia and reperfusion (62). In in vitro hypoxia models, DM reduces neuronal loss and dysfunction, which manifests as a decrease in the amplitude of anoxic depolarization (64). DM also attenuates the in vitro degeneration induced by acute glucose deprivation (65).

### 4.3. Anti-parkinsonian effects

NADPH oxidase, the primary producer of extracellular superoxide in microglial cells, has been proposed to contribute to the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (66, 67). In a study of the mechanisms underlying the neuroprotective activity of DM, DM was shown to have a significant protective effect against the dopaminergic toxicity induced by MPTP (67). Wild-type mice receiving daily MPTP injections exhibited a significant loss of dopaminergic neurons in the substantia nigra pars compacta, but DM treatment significantly attenuated the neuronal loss elicited by MPTP (67). Relative to the wild-type mice, NADPH oxidase–deficient mice exhibited a significant resistance to MPTP-induced DA toxicity (67). In addition, the neuroprotective effect of DM was observed only in wild-type mice, but not in NADPH oxidase–deficient mice, suggesting that NADPH oxidase is a critical target mediating the neuroprotective activity of DM in the MPTP mouse model.

Observing that MPTP-induced dopaminergic neurodegeneration is associated with reactive microgliosis, Gao et al. (66) proposed that inhibition of reactive microgliosis is the basis for the neuroprotective effect of DM against MPTP toxicity. In wild-type mice, the initial dopaminergic neuron-destroying effect of MPTP induces reactive microgliosis, which in turn activates NADPH oxidase through the translocation of cytosolic subunits to the cell membrane and the generation of superoxide. The neuroprotective effect of DM is attributed to its blockade of reactive microgliosis induced by DA neuronal death through the inhibition of both extracellular superoxide and intracellular reactive oxygen species (67).

In addition, DM blocks the MPTP toxicity–enhancing effect of the superoxide dismutase inhibitor diethyldithiocarbamate in mice (68). A histological analysis demonstrated that the depletion of dopaminergic neurons induced by the co-administration of diethyldithiocarbamate and MPTP is completely prevented by DM. DM also effectively prevents glutamate toxicity in mesencephalic cell cultures, as evaluated by the uptake of [3H]-labeled dopamine. DM shows the same pattern of protection as nicotine and MK801, both of which increase fibroblastic growth factor levels in the striatum, suggesting that DM might also work through a neurotrophic mechanism.

DM has also been found to reverse haloperidol-induced catalepsy in rats (69) and to potentiate the effect of levodopa and D1 (but not D2) agonists in reserpine-treated mice (70). However, conflicting results have been ob-
served in human studies (71, 72).

4.4. Effects on pseudobulbar affect

Pseudobulbar affect (PBA), also known as emotional lability, is characterized by frequent and inappropriate episodes of crying and/or laughing and is associated with neurological disorders such as stroke, amyotrophic lateral sclerosis, Alzheimer’s disease, Parkinson’s disease, and traumatic brain injury. As PBA has been proposed to arise (at least in part) from neurochemical dysregulation of serotonergic, dopaminergic, and/or glutamatergic neurotransmission (73), agents shown to be useful therapeutically against PBA will probably be found to modulate this altered state of neurotransmission.

DM is well established as a σ₁-receptor agonist that suppresses the release of excitatory neurotransmitters (74) and as an uncompetitive antagonist of the NMDA-sensitive ionotropic glutamate receptor (9). However, its therapeutic potential is limited by the fact that it is extensively metabolized by cytochrome P450 2D6 to DX, which is rapidly glucuronidated (6, 75) and unable to cross the blood-brain barrier (76). Concomitant dosing with quinidine, one of the most potent inhibitors of cytochrome P450 2D6 activity (77), at 5% – 10% of the arrhythmogenic dose increases and sustains the concentration of DM in plasma, thereby enhancing its potential for therapeutic efficacy (78).

Although the precise neuroanatomical basis of PBA is still in question, it is thought to involve the disruption of inhibitory signals descending from cerebral cortex to motor regions of the brainstem implicated in the regulation of emotional output (79) Recent evidence suggests that the severity of cerebellar disconnection is directly related to PBA onset (80, 81).

Interestingly, neurons in the brainstem and cerebellum are richly decorated with σ₁ receptors, suggesting that the effect of DM on emotional control is mediated, at least in part, through its interactions with these receptors. As a σ₁-receptor agonist, DM is expected to inhibit the release of glutamate, and as an uncompetitive NMDA-receptor antagonist, it is expected to suppress the response to excitatory neurotransmitters (80). However, the precise mechanism of action of DM/quinidine in the regulation of PBA remains uncertain.

The above findings expand the recent clinical evidence that DM/quinidine co-administration markedly reduces PBA frequency and severity with satisfactory safety and high tolerability, increasing patient quality-of-life (81).

4.5. Effects on pain sensation

NMDA can cause somatic and neuropathic pain. Upon tissue injury, pain transmission passes through Aδ- and C-sensory fibers to the dorsal horn neurons, causing the release of peptides and excitatory amino acids and activating NMDA receptors (82, 83). This hyperexcitability event can prolong and intensify the sensation of pain.

Although not widely used today as an analgesic, DM was initially considered a pharmacologic alternative to morphine for pain management (84). DM modulates the sensation of pain by reducing the excitatory transmission of the primary afferent pathways along the spinothalamic tract. This process occurs in the dorsal horn of the spinal cord, where DM blocks NMDA receptors, reducing the threshold for pain transmission via the Aδ- and C-sensory fibers (85). The activation of neuronal firing by NMDA receptors increases intracellular calcium levels (86). DM has been shown to reduce and regulate the influx of intracellular calcium through NMDA receptor–gated channels (87), thereby antagonizing the effects of excitatory amino acids and reducing the release of various peptides, such as glutamate and aspartate. Thus, it can ultimately lead to an overall reduction of pain sensation (83).

NMDA-receptor antagonists have been found to prevent the induction of central sensitization under experimental conditions (85). These preclinical observations have led to the hypothesis that NMDA antagonists might reduce postoperative pain (85). In fact, pretreatment with DM effectively reduces postoperative pain after tonsillectomy, and the pain is reduced not only at rest but also on swallowing, suggesting that DM prevents the development of central sensitization after tonsillectomy (88).

5. Neuroprotective effects of DM analogs with improved safety profiles

5.1. Neuroprotective potential of DF

Dimemorfan (DF, 3-methyl-17-methylmorphinan), an effective non-narcotic antitussive agent with a low incidence of adverse events (89), was discovered through extensive screening of morphinan analogs and was first used in Japan in 1975 (89, 90). Its antitussive action appears to arise from a direct effect on the cough center in the medulla. It does not induce any significant physical or psychological dependence (89), and its antitussive action is not affected by the opioid receptor–blocker levallorphan. Studies in animal models indicate that DF is up to three times more potent as an antitussive agent than codeine and is equivalent in potency to DM. Its other possible beneficial effects have been evaluated using diverse models of neurodegeneration. Interestingly, the evidence indicates that the recognition sites for DM and DF are identical or overlapping (55, 91).

Previous studies demonstrated that DF is a high-affinity ligand for the σ₁ receptor (Kᵢ = 151 nM) but not the PCP site (Kᵢ = 16798 nM) and has anticonvulsant properties
and 3-CM have high-affinity for $\sigma_1$ receptors to attenuate scopolamine- and $\beta$-amyloid peptide–induced amnesia in mice (92), possibly through its enhancement of hippocampal acetylcholine release (93). Our group has reported that the anticonvulsant effect of DF correlates with its $\sigma_1$-receptor–activated modulation of the AP-1 transcription factor (43, 55). Similarly, DF exhibits a protective effect against cerebral ischemia–reperfusion injury in rats through a $\sigma_1$-receptor–dependent mechanism that blocks glutamate accumulation and the downstream pathologic events that cause ischemic brain injury (94). In contrast, DF acts via $\sigma_1$-receptor–independent mechanisms to modulate intracellular calcium release, NADPH oxidase activity, and NF-κB signaling, inhibiting the expression of inducible nitric oxide (NO) synthase and the production of NO and pro-inflammatory cytokines. These activities may contribute to its anti-inflammatory properties and its protective effects against endotoxin shock in mice (95).

5.2. Anticonvulsant effects of other DM analogs

Some newly developed DM analogs have also shown promising anticonvulsant effects (20, 34, 96). In investigating the effects of a series of synthetic DM analogs (modified at positions 3 and 17 of the morphinan ring system: see Fig. 1) on maximal electroshock convulsions in mice, Kim et al. (34) found that DM, DX, 3-allyloxy-17-methylmorphinan (3-AM), and 3-cyclopropylmethylxoy-17-methylmorphinan (3-CM) had anticonvulsant effects, whereas 3-methoxymorphinan and 3-HM did not. According to these studies (20, 34, 96), DM, DX, 3-AM, and 3-CM have high-affinity for $\sigma_1$ receptors, but all have low affinity for $\sigma_2$ receptors. In binding to PCP sites, DX has a higher affinity than DM, whereas 3-AM and 3-CM have very low affinities, suggesting that PCP sites are not required for the anticonvulsant actions of 3-AM and 3-CM (34). These studies show that these new DM analogs are promising anticonvulsants that are devoid of PCP-like behavioral side effects and that their anticonvulsant actions may be, at least in part, mediated via $\sigma_1$ receptors (34, 55, 97).

5.3. Anti-parkinsonian effect of 3-HM

In structure–activity studies designed to find more potent neuroprotective DM analogs, 3-HM, a DM metabolite lacking methyl groups at the $O$ and $N$ sites, emerged as a novel candidate for the treatment of Parkinson’s disease (98). Zhang et al. showed that 3-HM is a more potent neuroprotective agent than its parent compound, DM, against lipopolysaccharide (LPS)-induced neurotoxicity and that it is neurotrophic to dopaminergic neurons in primary mixed mesencephalic neuron–glial cell cultures (98, 99). Furthermore, after showing that the neurotrophic effect of 3-HM is glial cell–dependent and that 3-HM fails to show any protective effect in neuron-enriched cultures, they subsequently demonstrated that it is the astroglial cells, and not the microglial cells, that contribute to the neurotrophic effect of 3-HM (98). This conclusion was based on reconstitution studies in which microglial or astroglial cells were added back to neuron-enriched cultures at various final percentages (10% – 20% and 40% – 50%, respectively); 3-HM was neurotrophic after the addition of astroglial cells but not microglial cells (98).

Conditioned medium from 3-HM–treated astroglial cells exerts a significant neurotrophic effect on dopaminergic neurons. 3-HM appears to induce the astroglia to release certain neurotrophic factors (i.e., epidermal growth factor, glial cell-derived neurotrophic factor, transforming growth factor-β1, and -α1, and activity-dependent neurotrophic factor) (98) that are responsible for its neurotrophic effects. As might be expected, in addition to the detrimental effect of Parkinson’s disease on DA neurons, a considerable glial reaction that is potentially protective takes place in the substantia nigra pars compacta in Parkinson’s disease. The glial cells (particularly the astroglia) protect stressed dopaminergic neurons by producing neurotrophic factors that counteract oxidative stress. One potential therapeutic avenue for Parkinson’s disease would be the stimulation of astroglial cells to produce these neurotrophic factors to rescue damaged or dying neurons.

In addition to its neurotrophic effect, 3-HM has an anti-inflammatory mechanism that is also important for its neuroprotective activity; in the reconstitution experiments of Zhang et al., LPS-induced neurotoxicity and 3-HM-mediated neuroprotection increased as the percentage of microglial cells added back to the neuron-enriched cultures increased (98). 3-HM provides potent neuroprotection by acting on two different cell targets: it has a neurotrophic effect mediated by astroglial cells and an anti-inflammatory effect mediated by inhibition of microglial cell activation. The higher potency of 3-HM relative to DM is attributable to the neurotrophic effect that occurs in addition to the anti-inflammatory effect shared by both substances (97, 98).

Zhang et al. (98) also observed a neuroprotective effect for 3-HM in both in vivo and in vitro studies using the MPTP model. In their in vitro system using primary mixed mesencephalic neuron–glial cell cultures, 3-HM (1 – 5 μM) significantly and dose-dependently attenuated the reduction in dopamine uptake induced by MPTP or its active component, 1-methyl-4-phenylpyridinium (MPP+). At the same concentrations, 3-HM also significantly increased the dopamine uptake capacity of the cells, confirming its neurotrophic effect. In their in vivo
studies, the administration of 3-HM significantly reduced the MPTP-induced loss of nigral dopaminergic neurons, as previously seen for DM. Significant depletion of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid is observed in the striata of MPTP-treated mice, and levels of all of these biogenic amines are attenuated in lesioned mice previously treated with 3-HM. The advantage of 3-HM over DM is the neurotrophic effect of the former, which may enhance the sprouting of dopaminergic terminal fibers in the striatum, accelerate the formation of dopamine-containing vesicles, assist the re-synthesis of dopamine after lesions, and eventually re-establish the return of the DA system to normal functioning. In addition, the anti-inflammatory effect exerted by 3-HM resulting from the inhibition of microgliosis generated from the MPTP/MPP+-damaged dopaminergic neurons is another important mechanism of 3-HM. 3-HM inhibits the reactive microgliosis in primary mesencephalic neuron–glial cells cultures after MPTP/MPP+ treatment (98).

Thus, in in vivo and in vitro MPTP models of Parkinson’s disease, 3-HM is beneficial both in reducing dopaminergic neuronal degeneration in the substantia nigra pars compacta and in reversing the depletion of biogenic amines in the striatum through dual mechanisms—a neurotrophic effect and the reduction of reactive microgliosis—consequently providing significant neuroprotection.

5.4. Anti-parkinsonian effect of GCC1290K, a 3-HM prodrug

To enhance the oral bioavailability of 3-HM, which is approximately 18%, we synthesized the 3-HM prodrug GCC1290K (Fig. 1), which has a much higher oral bioavailability of approximately 92%. The anti-parkinsonian effects produced by i.p. administration of 3-HM are comparable to those produced by oral administration of GCC1290K (data not shown). These findings are described in our PCT patent application WO/2008/111767A1 [“Orally bioavailable prodrug of (+)-3-hydroxymorph-
An Investigational New Drug Application for the prodrug (IND 107,477) has been approved by the United States Food and Drug Administration. GCC1290K is totally free from safety issues, as shown by studies using 3-HM (data not shown) and is now undergoing clinical trials.

5.5. Behavioral effects of DM analogs

The repeated administration of DM or its major metabolite, PCP-like DX, significantly increases locomotor activity and circling behavior, although these behavioral responses are less pronounced than those caused by PCP. These behavioral responses are enhanced much less by DF and 3-HM (or GCC1290K) than by DM and DX. In terms of behavioral effects, DM, DX, and PCP produce significant behavioral side effects (i.e., CPP and locomotor stimulation), but DF and 3-HM (or GCC1290K) produce very few behavioral side effects (as seen in DM- or DX-treated animals), suggesting that DF and 3-HM have negligible psychotropic effects (34, 97, 98).

6. Conclusions

The research findings discussed in this review demonstrate that DM produces neuropsychotoxic effects and has a potential for abuse, although it also has diverse positive effects. In addition, the evidence suggests that DM and its analogs offer strong neuroprotective benefits in multiple neurodegenerative disorders through their antioxidant, anti-inflammatory, and neurotrophic effects and through their modulation of the interactions between NMDA, PCP, and \( \sigma_1 \) receptors (refer to Fig. 3 and Table 1). Thus, they offer a promising new direction for the development of therapeutic compounds for the treatment of excitotoxic and inflammatory neurodegenerative disorders.

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Table 1. Neuropsychopharmacological profiles of DM and its analogs

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References

27. Malenfant SA, O’Hearn S, Fleming AS. MK801, an NMDA antagonist, blocks acquisition of a spatial task but does not block maternal experience effects. Physiol Behav. 1991;49:1129–1137.


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