[12:00～12:40]

Neuroprotective action of dextromethorphan analogs with negligible psychotomimetic Effects

Hyoung-Chun Kim, Ph.D.

Neurotoxicology Program, College of Pharmacy, Kangwon National University, Chunchon 200-701, KOREA.

Dextromethorphan (DM; 3-methoxy-17-methylmorphinan) is a non-narcotic morphinan derivative widely used as an antitussive for almost 40 years. It has been attracted attention due to its neuroprotective properties. However, case reports of toxicity in children, and phencyclidine (PCP)-like psychotomimetic reactions associated with high-dose DM ingestion are likely attributable to dextrorphan (DX; 3-hydroxy-17-methylmorphinan; a major metabolite of DM. The DM dose for the neuroprotective effects is much higher than the cough suppressant dosage. Clinically, high doses of DM can produce psychotropic effects. Furthermore, DM has been recognized as the object of drug-seeking behavior in Korea and several countries. Our laboratory suggested that DM potentiates the psychotropic effects induced by cocaine, and that DM itself might produce psychotoxic effects in mice. Moreover, we have demonstrated that chronic DM administration perturbs the cellular immune response, and this is similar to the immunosuppressive effects caused by PCP. In this study, we observed

the neurotoxicity induced by high-dose DM. Treatment with DM induced condensed chromatins (electron dense particles), vacuolated stacks of endoplasmic reticulum and mitochondrial swelling with disrupted cristae in the retrosplenial/cingulated cortex and hippocampus of the rats. These neuropathological changes were, in part, similar to those induced by the cyclohexamines (i.e. MK-801, ketamine and PCP). However, this finding was not observed in the animals treated with DX. DM-induced neurotoxicity was significantly attenuated by the pre-treatment with MK-801 or nifedipine, suggesting that DM might have the properties of a mixed agonist that might act as a NMDA receptor antagonist at a low dose, or of a channel activator at a high dose that might act as as a L-type calcium channel blocker at a low dose.

In the past decade, investigators have documented that DM has an N-methyl-D-aspartate (NMDA) receptor antagonistic effect with neuroprotection. Therefore, a DM analogue that retained its neuroprotective activities without exerting neurotoxicity or being converted into DX *in vivo* would be highly useful.

Recently, we synthesized a series of compounds that are modified in positions 3 and 17 of the morphinan ring system, with the intention of developing compounds that retain anticonvulsant activity/neuroprotective property with negligible psychotropic effects (Fig. 1.). To reduce the PCP-like behavioral side effects, while retaining the

anticonvulsant/neuroprotective effects, we prepared a series of 3- and 17-substituted morphinans that are structurally similar to DM, but are either not expected to be metabolized into DX or are expected to do so at a reduced rate compared to DM.

We employed an automated video-tracking system to measure locomotor activity and pattern and the conditioned place preference paradigm in order to assess the behavioural effect (behavioural safety) mediated by morphinans, such as DM, 3-hydroxymorphinan (HM), 3-allyloxy-17-methylmorphinan (AM), 3-cyclopropylmethoxy-17-methylmorphinan (CM) and dimemorfan (DF; 3-methyl-17-methylmorphinan).

We demonstrated that the mechanism of anticonvulsant / neuroprotective action of AM, CM or DF might be mediated via σ_1 receptors rather than PCP sites. The very low affinity of AM, CM or DF to PCP sites also provides evidence that acting on PCP sites might not be a prerequisite for the anticonvulsant / neuroprotective effects of morphinans. Although DM, AM, CM and DF exhibited anticonvulsant effects, HM did not show any anticonvulsant effect in response to kainate or maximal electric shock, suggesting that pharmacological action of HM may be specific on the dopaminergic system. DM is rapidly metabolized by O-demethylation to a PCP-like compound, DX. DX then undergoes N-demethylation yielding HM. Both DX and HM are eliminated

after glucuronidation. Alternatively, DM is metabolized first by N-demethylation yielding 3-methoxymorphinan, which then undergoes an O-demethylation reaction to yield HM. These metabolic processes may be helpful in attenuating dopaminergic toxicity, although more evidence should be gathered. We assumed that 3-methoxymorphinan and HM have lower CNS activity as compared with DM or DX, but the route-specific effects of morphinan administration, influence of morphinan dosage, and *in vivo* glucuronidation capacity should be considered.

It has been suggested that low-affinity NMDA open channel antagonists may be antiparkinsonian drugs. DM has a complex pharmacological profile that includes a micromolar affinity for the NMDA receptor channel. In two open-label clinical trials, DM was founded to afford significant improvement in small cohorts of parkinsonian volunteers. It was demonstrated a modest recovery of activity in reserpinized mice following injection of DM and ketamine, but these were subject to considerable inter-animal variation.

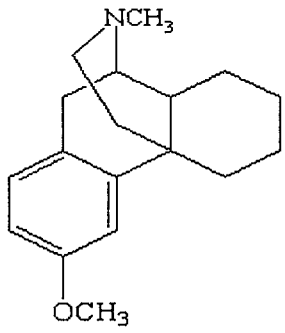
A major objection to administering NMDA receptor antagonists to man is that they can cause unacceptable side effects. These include psychostimulation and memory impairment, as well as muscle relaxation and ataxia. From theoretical considerations, however, compounds which have a low affinity for the NMDA receptor-associated ion

channel may be the most effective and the least toxic of the of the many NMDA receptor antagonists that are available. Among the NMDA receptor antagonists, DM appears to be matched this theoretical ideal and has been tested in small groups of idiopathic parkinsonian patients with mixed success. Earlier reports have indicated that NMDA receptor blockade can directly restore motility to Parkinson-like mice and rats, but not primates. However, not all laboratories find this and the matter is subject to some controversy.

In contrast, dextromethorphan analogs HM, AM, CM and DF used in this study, had very low affinities for NMDA receptor associated PCP sites, suggesting that NMDA associated PCP sites are not prerequisites for their antiparkinsonian actions. In addition, previous reports indicated that DM, DX, HM, AM, CM and DF are high affinity ligands at σ_1 receptors. Further it is recognized that σ_1 receptors regulate glutamate NMDA receptor function and release of dopamine. Selective σ_1 receptor ligands have been suggested to present a new class of therapeutic agents for neurodegenerative diseases, although none have yet been introduced into therapeutic use. In addition, σ_1 receptor plays an important role in the facilitation of dopamine transmission. This phenomenon is partially involved in the augmentation of dopamine synthesis rate. Although we cannot exclude morphians' contribution via NMDA

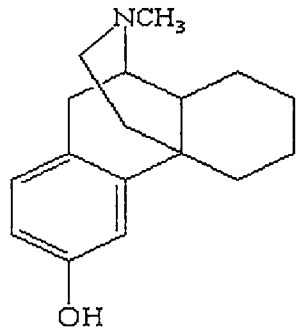
receptor antagonism, we suggest that the primary mechanism of action of morphinans is, at least in part, related to σ_1 receptor modulations. The pharmacological actions induced by these morphinans must be further explored *in vivo*.

Combined, the results of this study indicate that DM has prominent anticonvulsant and antiparkinsonian effects, although DM has behavioral side effects. More importantly, the other morphinans do not produce the PCP-like behavioral side effects and neurotoxicity induced by DM. AM, CM, and DF possess a novel anticonvulsant effect. In contrast, HM and CM have significant antiparkinsonian effects in response to 1-methyl-4-phenyl-1,2,5,6-tetrahydropridine (MPTP), lipopolysaccharide (LPS) and methamphetamine (MA). Although AM and DF are effective against MA-induced neurotoxicity, their potential pharmacological actions should be re-evaluated, since MA-induced dopaminergic toxicity has long been considered to be one of the most important animal models of Parkinson's disease. Finally, additional mechanisms mediated by morphinans will be discussed in this presentation [This research was supported by a grant (# M103KV01000803K2201 00820) from brain research center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology, Republic of Korea].



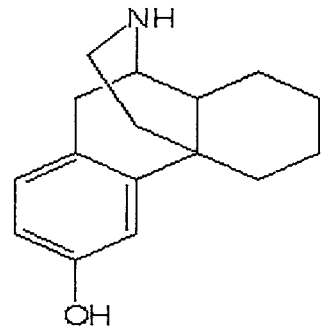
Dextromethorphan

(DM)



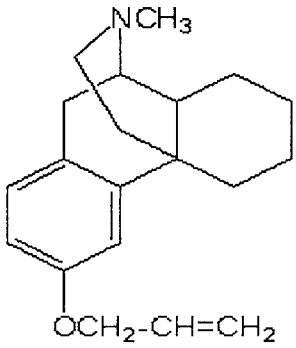
Dextrorphan

(DX)

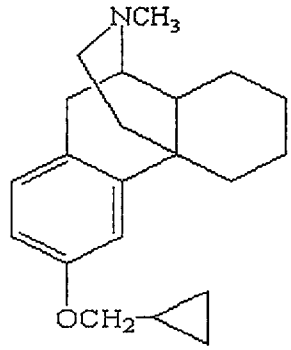


3-Hydroxymorphinan

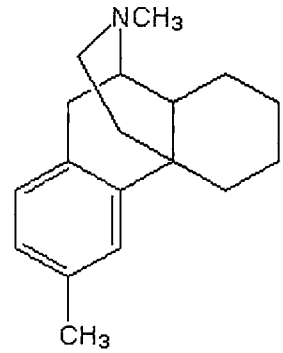
(HM)



3-Alloxy-17-methoxy-morphinan (AM)



3-Cyclopropyl-17-methoxy-morphinan (CM)



3-Methyl-N-methyl-morphinan (DF)

Fig. 1. Chemical structures dextrorotatory morphinan analogs (Kim et al. 2001).