Evaluation of the differential effects of MK-801 and MMP-2200 on dopamine receptor 1- and 2-agonist-induced abnormal involuntary movements

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I. ABSTRACT

The specific aim of this study was to measure the severity of dopamine receptor 1 (D1R) and dopamine receptor 2 (D2R)-induced abnormal involuntary movements (AIMs) when administered with the NMDA receptor antagonist MK-801 or opioid glycopeptide MMP-2200.

Methods

Male Sprague-Dawley rats were injected with 6-hydroxydopamine in 0.02% ascorbic acid into 2 locations in the medial forebrain bundle at the coordinates: AP: -2.8, ML: -1.8, DV: -7.9; (1, 3) Two-week post-surgery, rats that averaged at least 4 amphetamine-induced rotations were injected with levodopa (7.0 mg/kg) and benserazide (14 mg/kg) for 21 consecutive days to produce levodopa-induced dyskinesia. (3)

Rats were then primed with D1R agonist SKF81297 (0.8 mg/kg, s.c.) and D2R agonist quinpirole (0.2 mg/kg, s.c.) and verified the AIMs scores were stable.

MK-801 and MMP-2200 significantly reduced D2R-induced AIMs but significantly reduced D2R-induced locomotor AIMs by 50%. MMP-2200 significantly reduced D2R-induced LAO AIMS by 45% and D2R-induced locomotor AIMS by 90%.

II. PURPOSE

To evaluate the effects of MK-801, an NMDA receptor antagonist, and MMP-2200, a mixed mu and delta opioid receptor agonist, on dopamine receptor 1- and dopamine receptor 2- induced abnormal involuntary movements (AIMs).

III. METHODS

Main Results

MK-801 worsened D1R-induced limb, axial and orolingual (LAO) AIMs (p<0.005) whereas there was no change in locomotor AIM scores. MK-801 reduced D2R-induced LAO AIMs by 89% (p<0.001). MK-801 induced orolingual involuntary movements, which is a parkinsonian symptom in this preclinical rat model. The rats were first primed with the D1R agonist SKF81297, then co-administered with MK-801 or MMP-2200 and AIM scores were recorded to determine the severity of the dyskinesia. Then the same procedure was performed with the D2R agonist quinpirole.

Conclusions

Both MK-801 and MMP-2200 had differential effects on the rotter direct and indirect striatofugal pathways with regards to AIMs. These results support that glutamate is a key neurotransmitter contributing to AIMs.

V. SUMMARY

• HPLC-EC and semi-quantitative western analysis confirmed unilateral loss of DA in the lesioned side.
• MK-801 significantly worsened dystonia in D1R induced AIMS and did not effect limb, orolingual, or locomotor AIMs.
• MK-801 significantly reduced LAO AIMS by 89%. Individual analysis showed significant decreases of limb, orolingual, and axial AIMs by 84%, 97.5%, and 72%, respectively.
• MK-801 induced orolingual involuntary movements in D2R induced AIMS, which represent parkinsonian symptoms.
• MMP-2200 did not effect D1R induced LAO AIMS but significantly reduced D2R induced locomotor AIMs by 50%.
• MMP-2200 significantly reduced D2R-induced LAO AIMS by 45% and D2R-induced locomotor AIMs by 90%.

VI. CONCLUSIONS

Both MK-801 and MMP-2200 show differential effects on the direct and indirect striatofugal pathways with regards to AIMs.

These results support that glutamate is a key neurotransmitter contributing to AIMs.

VII. REFERENCES


VIII. DISCLOSURE

The authors of this presentation have nothing to disclose.