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Effects of Dextromethorphan On MDMA-Induced Serotonergic Aberration In The Brains of Non-Human Primates Using [123I]-ADAM/SPECT

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Effects of Dextromethorphan On MDMA-Induced Serotonergic Aberration In The Brains of Non-Human Primates Using [123I]-ADAM/SPECT

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Abstract Abstracted

MDMA (methylenedioxymethamphetamine) is a very commonly used recreational drug. MDMA is in a class of drugs known as entactogens. These are “psychedelic stimulants.” MDMA is an extremely strong agonist of serotonin and dopamine and is known to induce serotonergic neurotoxicity in the brain. Dextromethorphan is a widely prescribed antitussive (used to reduce coughing) and has demonstrated anti-inflammatory effects in vivo.

This study investigated the effects of MDMA on the serotonergic system in primates after long-term use. The study then evaluated the possible protective effects of DXM against the abnormalities in the serotonin system induced by the MDMA. Nine Macaca cyclopis monkeys were divided into: Control, MDMA treatment, and the co-treatment group which received MDMA and DXM. The study uses SPECT scans (single positron emission tomography) to image the abnormalities. These scans utilized a special radioligand known as [123I]-ADAM for serotonin transporters (SERTs). Brain SERT levels were quantified as uptake ratios (UR’s) of the [123I]-ADAM in certain brain regions, including the midbrain, thalamus, and striatum.

The results of this study revealed that the MDMA treated monkeys had a significantly lower uptake of the [123I]-ADAM when compared to the control group, indicating that MDMA reduced SERT levels. This decrease persisted for over four years following the treatment. However, the co-treatment group did not exhibit a loss of brain SERT levels, indicating that the DXM may have a protective effect against MDMA-induced serotonergic toxicity in the brains of non-human primates.

The Pharmacology of MDMA

- MDMA enters neurons through SERTs and inhibits the vesicular monoamine transporter 2 aka VMAT2.
- VMAT2 normally cages 5-HT (serotonin) into intracellular vesicles.
- MDMA's presence allows serotonin to accumulate in the cytosol.
- MDMA reverses the normal direction of the serotonin transporters which causes its exportation from the neuron and even blocks its reuptake.
- Serotonin begins to accumulate in the synaptic cleft.
- MDMA inhibits the transporters responsible for dopamine and norepinephrine, so this leads to an extraneuronal increase in these neurotransmitters as well.

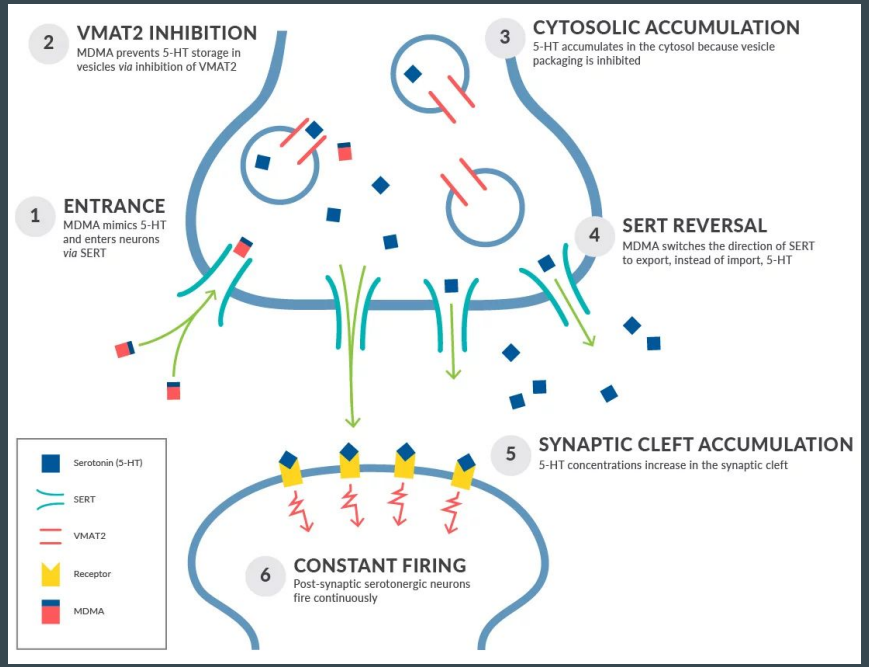


Figure: The mechanism of action of MDMA in a serotonergic neuron. (MDMA from Rave Drug to Rave Reviews in Clinical Trials, n.d.)

The Pharmacology of DXM (Dextromethorphan)

- DXM is most widely used to reduce coughing during a cold.
- Its main mechanism of action is proposed to be on the nucleus tractus solitarius. This is the site where pulmonary vagal afferent fibers synapse into the central nervous system. In other words, this is where the cough reflex comes from.
- DXM is structurally similar to opioids, yet does not have any direct action on the opioid receptors that are involved in producing the classic opioid effects.
- DXM's main site of action that is known is on N-methyl-D-aspartate (NMDA) receptors as a non-competitive antagonist.
- DXM is also an inhibitor of serotonin transporters, norepinephrine transporters, and voltage gated ion channels.

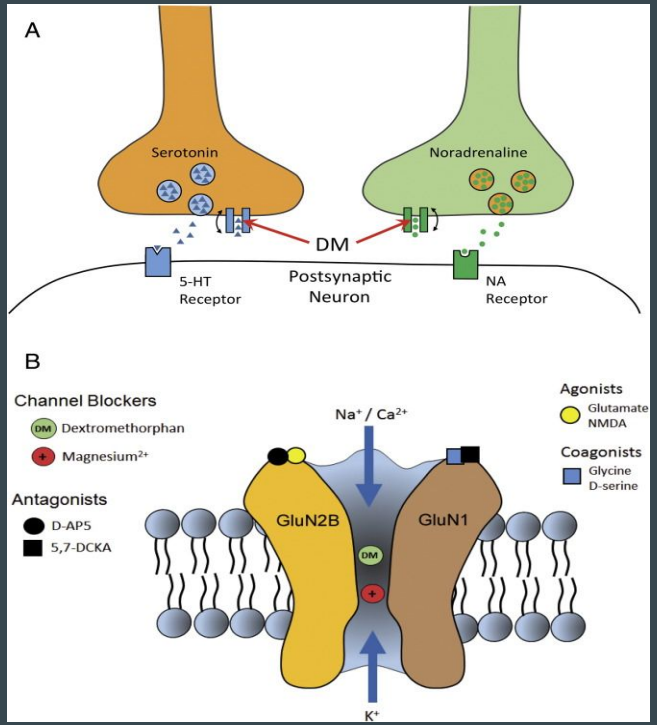


Figure: Summary of DM molecular sites of drug action in human brain.
(Taylor et al.)

Methods

- The study involved nine Formosan rock monkeys (Macaca cyclopis) weighing approximately 5–8.5 kg.
- Environmental conditions such as temperature, humidity, and a 12-hour light/dark cycle were kept constant.
- MDMA and DXM were both dissolved in saline for subcutaneous injection.

Procedure

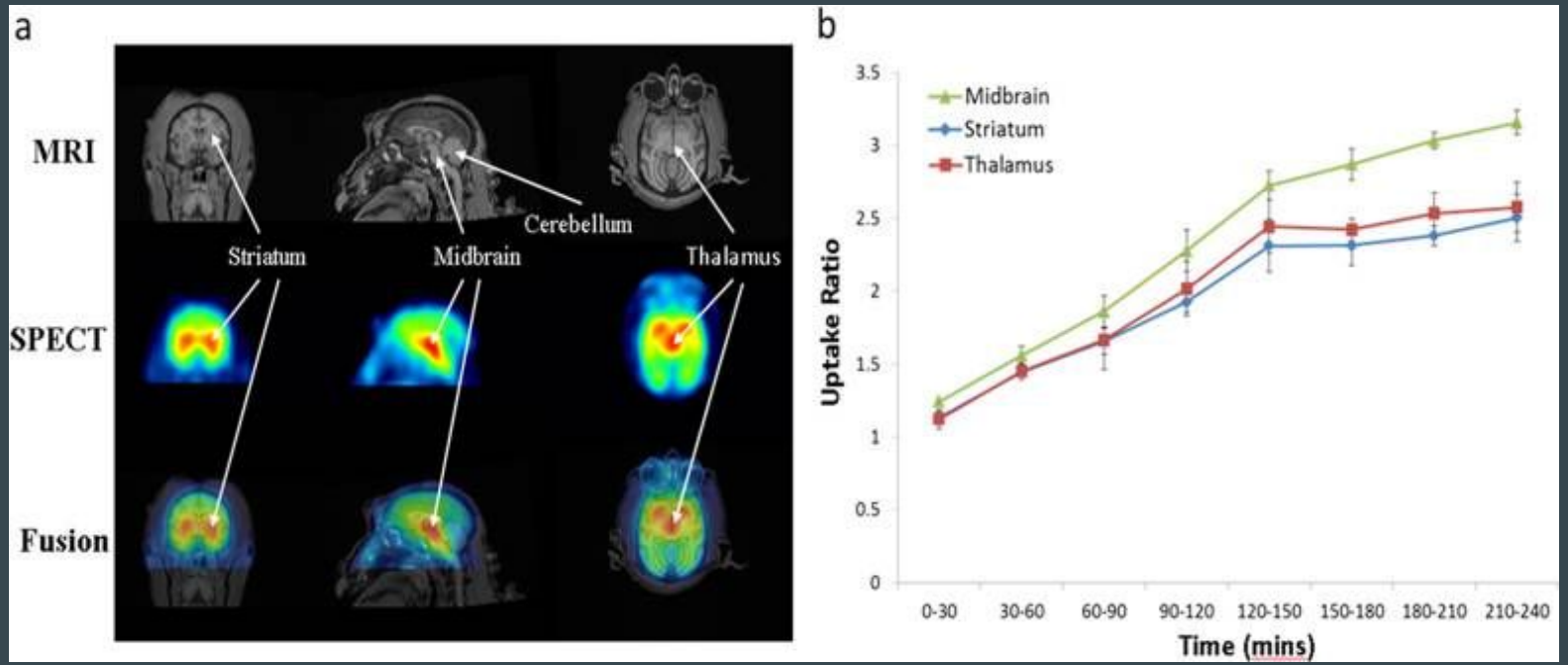
- MDMA and DXM were both dissolved in saline for subcutaneous injection.
- Monkeys did not eat overnight and were anesthetized with ketamine (10 mg/kg).
- They received passive inhalation of oxygen, keeping oxygen saturation 99.5%.
- Radiotracer administration was done via intravenous infusion through the cephalic vein using 0.9% NaCl.
- Potassium perchlorate (200 mg) was administered orally 20 minutes prior to radiotracer injection to minimize thyroid uptake of 123I.
- All drugs were administered twice daily for 4 consecutive days.
- [123I]-ADAM injections were performed at approximately 4-week intervals.
- In the co-treatment group, DXM (5 mg/kg) and MDMA (5 mg/kg) were given twice daily for four consecutive days
- The DXM was administered 5 minutes prior to the MDMA.
- SERT imaging was measured at 1, 4, 24, 30, 48, and 54 months to evaluate the long-term effects of MDMA/DXM
- The [123I]-ADAM tracer was synthesized at The Institute of Nuclear Energy Research, Lung-Tan, Taiwan.

SPECT Analysis In Monkey brain

- As soon as the [123I]-ADAM was injected, the imaging began.
- It was performed on a rotating camera equipped with ultra-high resolution fan-beam collimators
- The SPECT images were created by reconstructing the data from every scan per 30 min over the full 4-h course of the experiment using a Metz filter.
- All SPECT data were acquired by the same investigator to avoid bias.
- Regions of interest were MRI'd.
- MRI images were resliced, resized, and coregistered with all corresponding SPECT images in planes parallel to the canthomeatal line.
- The uptake ratios (URs) were calculated by dividing the mean counts per pixel in the target area (MB, TH, or ST) by the mean counts per pixel in the CB.

Results: MRI, SPECT images and [123I] -ADAM Uptake ratios (URs)

The results of the imaging procedures showed that there was the most uptake in the midbrain, followed by the striatum and the thalamus, and almost none in the cerebellum.

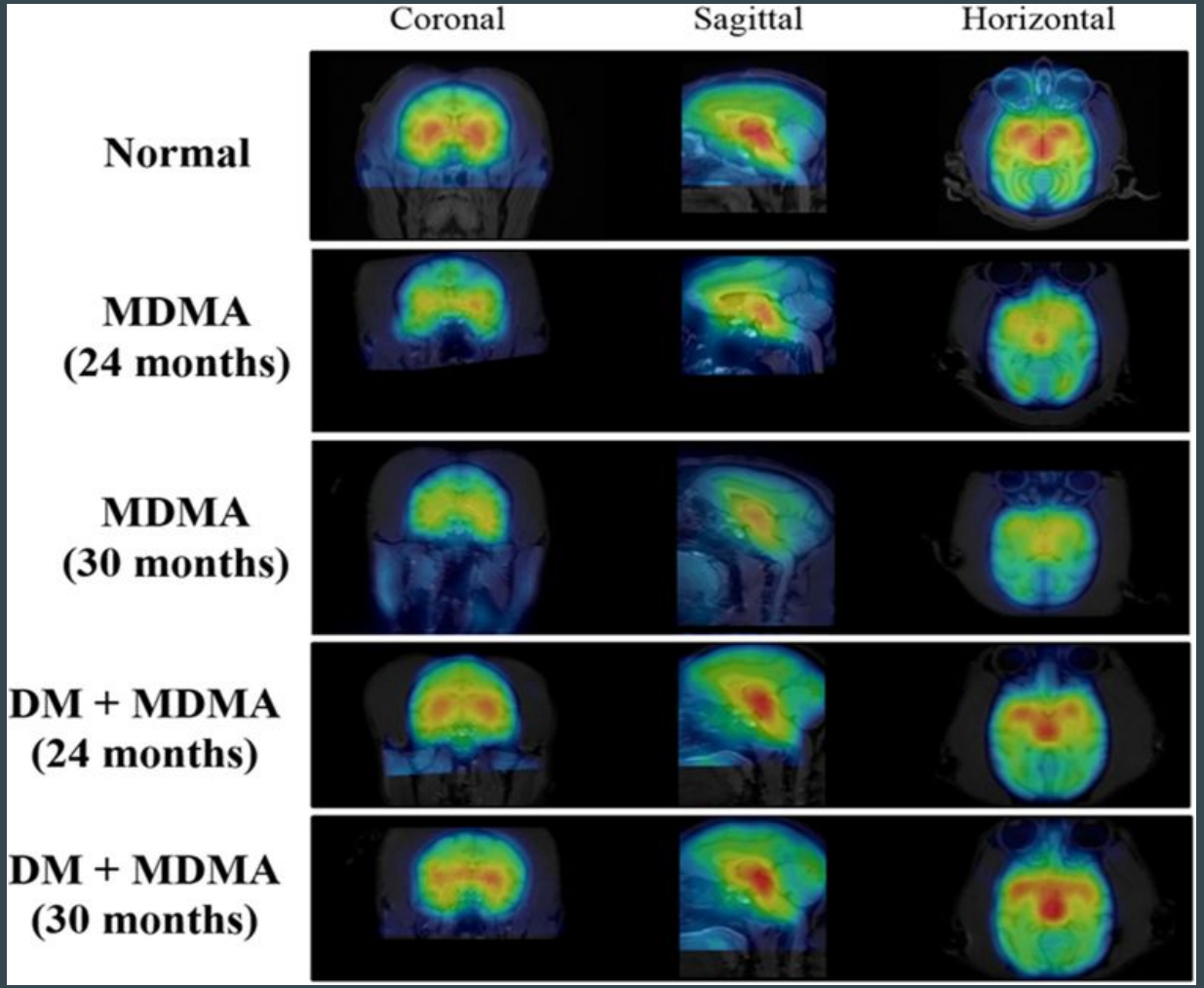


(a) Representative images of MRI and [123I]-ADAM/SPECT in coronal (left column), sagittal (middle column) and horizontal (right column) views. (b) UR's of [123I]-ADAM in the midbrain, striatum and thalamus at different time points in normal monkeys.

Results: MDMA Induced Abnormalities

- A SPECT scan of the monkeys' brains were performed to assess the influence of MDMA on the serotonin system.
- The scans showed significantly decreased uptakes of the [123I]-ADAM ligand in the striatum, thalamus, and midbrain compared to the control group.
- The average uptake ratios of the tracer ligand in the three brain regions increased over time after the MDMA treatment and gradually reached a plateau after about 2 hours.
- The treatment group values were 1.64 ± 0.03 in striatum, 1.88 ± 0.05 in thalamus and 2.24 ± 0.03 in midbrain.
- In the control group, the values were 2.50 ± 0.22 in striatum, 2.62 ± 0.21 in thalamus and 3.16 ± 0.17 midbrain.
- These abnormalities lasted up to 24 months.
- The average uptake ratios in the DXM+MDMA monkeys at 24 months were 2.30 ± 0.19 in striatum, 2.38 ± 0.23 in thalamus and 2.85 ± 0.26 in midbrain.
- These were similar values to the control group.
- This indicates that MDMA induced serotonergic abnormalities can be abolished by DXM.
- This effect lasted up to 30 months.

Figure: MRI and [123I]-ADAM SPECT fusion images in coronal, sagittal and horizontal views at different time points in normal, MDMA and DXM+MDMA groups.



Discussion Pt. 1

- Several studies have shown that repeated exposure to MDMA leads to brain deficits, including neuronal death and memory loss specifically involving serotonin transport issues.
- MDMA-treated rodents had significantly lower URs of [123I]-ADAM in various brain regions compared to normal controls, indicating damage and decreased density of cerebral SERT in the serotonergic neurotransmitter system.
- The results of the study indicate that MDMA-induced damage, associated with reduced density of cerebral SERT, can persist over four years in the brain of non-human primates.
- Introducing MDMA into the neuronal space triggers a rapid accumulation of hydrogen peroxide, a byproduct of 5-HT metabolism involving monoamine oxidase B (MAO-B).
- H2O2 can be converted into OH- radicals and cause oxidative stress/damage to the mitochondria of serotonergic neurons.
- Since MDMA mimics serotonin, SSRIs could prevent MDMA from binding to SERT on presynaptic terminals.

Discussion Pt. 2

- In vivo models of ischemic brain injury have shown that DXM protects the brain against infarction and functional consequences of injury.
- The protective effects of DXM on MDMA-induced abnormalities lasted for about two and a half years.
- In vivo models of ischemic brain injury have shown that DXM protects the brain against infarction and functional consequences of injury.
- DXM may act similarly to SSRIs by inhibiting the binding of MDMA to SERT.
- DXM may protect against MDMA-induced damage by promoting or allowing dendritic spine maintenance as an antagonist of the NMDA receptor.
- The URs of the co-treatment group were notably higher than those of the MDMA-treated group.
- These results suggest that MDMA-induced serotonergic abnormalities persisted for over four years in non-human primates, and DXM could alleviate this abnormality.

Conclusion

Through SPECT scans utilizing [123I]-ADAM as the radioligand for serotonin transporters , the study observed significantly lower uptake ratios of [123I]-ADAM in the brains of monkeys treated with MDMA compared to the control group, indicating a decrease in brain SERT levels induced by MDMA.

Remarkably, this reduction in brain SERT levels persisted for over four years. However, in the co-treatment group, the loss of brain SERT levels was not observed, suggesting a potential protective effect of DXM against MDMA-induced serotonergic toxicity in the primate brain.

Further research into the therapeutic potential of DXM in protecting against the effects of MDMA on the serotonergic system is a must. MDMA has massive treatment potentials in the field of psychiatry, specifically for things like PTSD. However, the safety of recurrent use of MDMA comes into question. If DXM could make treatment with MDMA safer, this could be a real breakthrough in the psychiatric field.

Discussion Questions

Do you think that DXM would have the same protective properties as it does in the monkey brain in human brains? If so, how do you justify that?

“Magic Bullets” are a concept in philosophy of medicine that describe pharmaceutical drugs that treat only what they are designed to treat without having other effects. Oxycontin, for example, was marketed as such a drug specifically for pain. Though, opioids obviously affect much more than pain. Do you believe it is possible to design a drug that could be considered a magic bullet for the treatment of psychiatric disorders such as PTSD or depression?

Citations

Pharmacology of MDMA:

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Original Research Article:

Ma, Kuo-Hsing, et al. “Effects of Dextromethorphan on MDMA-Induced Serotonergic Aberration in the Brains of Non-Human Primates Using [123I]-ADAM/SPECT.” Scientific Reports, vol. 6, no. 1, Dec. 2016, https://doi.org/10.1038/srep38695. Accessed 26 Apr. 2022.