ST, ergotamine and analogues

PsychoTropical Commentaries: 2014:11;3

Ergotamine, bromocriptine and LSD

This is an interesting and obscure aspect of the serotonin toxicity saga, yes, it really is a saga. One of my mentors was Mervyn Eadie, Professor of Neurology in Brisbane. He has written some fascinating historical papers. One of them is '*Convulsive ergotism: epidemics of the serotonin syndrome'* [1]. His observation below, '*Dihydroergotamine given to human beings can cause the serotonin syndrome*', refers to the case reported by Mathew, related to IV use, which is rare **now [2]**.

He suggests, 'The serotonin syndrome may, therefore, have been a public-health problem long before it was recognised as a complication of modern psychopharmacology'. I quote Professor Eadie's whole abstract:

> 'Between 1085 and 1927, epidemics of "convulsive ergotism" were widespread east of the Rhine in Europe due to consumption of grain contaminated with ergot, which is produced by the fungus Claviceps purpurea. West of the Rhine, consumption of ergot-contaminated food caused epidemics of gangrenous ergotism. The clinical features of convulsive ergotism—muscle twitching and spasms, changes in mental state, hallucinations, sweating, and fever lasting for several weeks—suggest serotonergic over stimulation of the CNS (i.e., the serotonin syndrome). The ergot alkaloids are serotonin agonists. Dihydroergotamine binds to serotonin receptors in the dorsal horn of the spinal cord, which is the site of neuropathological changes in convulsive ergotism. Dihydroergotamine given to human beings can cause the serotonin syndrome. Ergots produced by different strains of Claviceps purpurea, and those growing in different soils, may have different ergot alkaloid compositions. An alkaloid, present in high concentrations in ergots from east of the Rhine, may have caused convulsive ergotism at a circulating concentration insufficient to produce peripheral ischaemia. The serotonin syndrome may, therefore, have been a public-health problem long before it was recognised as a complication of modern psychopharmacology.'

The following account of the clinical picture of convulsive ergotism given by Eadie is mainly derived from Tissot and Barger [3, 4].

> After a short period of vague illness, perhaps with some gastrointestinal symptoms, the first manifestation of the disorder was an abnormal sensation in the limbs, mainly the legs, which was described as feeling like ants crawling over the skin. Local pain then developed in the limbs. The initial features as ergotism developed were convulsive in nature: distortion of the trunk and limbs, painful involuntary flexion of the fingers and wrists, and either flexion or extension of the ankles. People with the disease were drowsy, sometimes delirious, lethargic, and melancholic or manic and could have hallucinations and double vision. Some affected individuals developed profuse sweating, fever, muscle stiffness, and twitching. … it seems likely that some of the involuntary postures would now be classified as torsion dystonia or other dyskinesias, … Involuntary movements and postures were, in some cases, followed by epileptic seizures, which were indicative of a fatal outcome.

However, reading this with our current understanding of serotonin toxicity, it seems to show more differences than similarities, and what we now regard as key symptoms are not convincingly described. The features are more suggestive of dopaminergically mediated dystonias. The cases described by Mathew are similarly atypical.

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Conclusion

There is no evidence that (Dihydro)ergotamine is involved in serotonin toxicity.

Bromocriptine

Bromocriptine is related to the other ergot derived dopamine agonists pergolide and cabergoline. It is a dopamine agonist and there is no evidence it is able to raise brain 5-HT. I have commented on cases where it also seems to have worsened serotonin toxicity that was mis-diagnosed as neuroleptic malignant syndrome and was treated as such (16): bromocriptine 'has frequently been used to treat NMS, has been reported to increase brain 5-HT levels with the attendant risk that this could conceivably (I do not think this is likely, and the evidence is poor) worsen SS when it is confused with NMS. An example of such a case may be that of Kline et al. [5] where treatment with dantrolene and bromocriptine was given to a patient with SS and the temperature then rose from 38.1 8C to 42.2 8C within 3 h and death ensued'. Other cases where this may be relevant are: [6-10].

LSD (lysergic acid diethylamide)

Usual doses of LSD (whatever that means) are not associated with serotonergic symptoms or features of serotonin toxicity, neither are large doses or over-doses. First one may note that in more than 50 years of use there are no reported typical cases of serotonin toxicity, as is also the case with the structural analogues, bromocriptine and ergotamine.

The best report of which I am aware is of 8 people who had simultaneously ingested large doses of LSD and some cocaine [11]. Some of them became hyperthermic, but the seemingly good clinical description does not include typical serotonin toxicity symptoms. There are other case reports, but again with no signs of serotonin toxicity [12, 13].

Agonist/Ligand - directed signalling/trafficking

A recent summary of the putative mechanisms of action of LSD supports a role for the 2A receptor [14]. This leads to a consideration of the concept of agonist directed signalling, which is complex and beyond the scope of this commentary. Nevertheless, it is clear that agonists at the 5HT2A receptor can produce different downstream signals. That may explain why LSD can elicit hallucinations, but not hyperthermia, as would be expected as part of the serotonin toxicity picture — because that is what happens when excessive amounts of the endogenous ligand, 5HT, activate that receptor. Fantegrossi et al, state:

> Relative to the endogenous ligand 5-HT, in NIH3T3-5HT2A cells, LSD stimulates the PLA2 pathway to a greater extent than the PLC pathway.

Banerjee et al. [15] have shown

> ...distinct signaling signatures, differing in magnitude and kinetics, at the 5-HT2A receptor, in response to DOI versus lisuride [which is thought to be less likely to provoke hallucinations than LSD].

Human data

Professor Whyte states [personal communication] that as of early 2008

> 'We have seen only a few LSD overdoses locally and none of 21 admissions developed significant serotonin toxicity even though several had co-ingested MDMA and one had taken MDMA and tramadol as well as LSD. Thus while LSD could theoretically produce ST it does not seem to be very common.'

Conclusion

There is no evidence that bromocriptine or LSD are involved in serotonin toxicity.

References

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