Global Science Research Journals

Available online at
www.globalscienceresearchjournals.org

Global Journal of Medicine and Medical Sciences

ISSN: 2449-1888. Vol. 9 (1). Pp.1-3
December, 2020

Short Communication Open Access

Alterations in brain Nitric Oxide (NO) in LSD Hallucinations and Psychosis

Nicola Petrogalli

Department of Mechanical Engineering, University of Brescia, Brescia, Italy

Corresponding author. E-mail: n.petrogalli@studenti.unibs.it

Received 7 December 2020; **Accepted** 21 December, 2020; **Published** 28 December 2020

ABSTRACT

The main neurotrasmitter involved in psychosis is dopamine, but recent findings show that the alteration of the dopaminergic neurotransmission may be secondary to Nitric Oxide (NO) dysfunction. LSD Hallucinations are due to a diminished cerebral blood flow (CBF) in some brain regions, such the ones belonging to the Default Mode Network (DMN), and an enhanced CBF in regions which usually don't communicate. This is the reason why the brain works in a chaotic way under the effect of LSD. The main molecule which controls the physiology of Cerebral Blood Flow is Nitric Oxide, which is necessary altered in a brain under the effect of LSD.

Since LSD Hallucinations can be seen as an experimental model of induced psychosis, this paper extends such a role of NO in determining unconventional neural pathways also in psychosis, providing for the first time a possible mechanism beneath this pathological condition.

Keywords: Nitric oxide, LSD, Psychosis, Schizofrenia, Default mode network, Cerebral blood flow

HALLUCINATIONS BY LSD

LSD-25 (Lysergic Acid Diethylamide) is a hallucinogenic molecule capable to heavily alter the human consciousness.

Hofmann synthesized LSD in 1938, but only in 1943 he accidentally (probably throught his hands) took a small quantity which determined visions of "an uninterrupted flow of fantastic figures, extraordinary shapes which revealed intense kaleidoscopic colour effects"(Albert Hofmann, 2015). After few days, Hofmann decided to voluntarily assume the substance in order to experiment its effects, taking a 250 micrograms dose (without his knowledge a high dose, since the minimum dose for hallucinations in order to happen is 25 micrograms) and after half an hour referred about very colorful and wonderful, monstrous, geometric, grotesque visions, perception of parallel worlds, terror, euphoria, hypersensitivity and detachment from reality.

Initially, LSD was used as a psychiatric drug, since the substance was capable to induce an "Experimental psychosis". There were also two therapeutic approaches based on the use of LSD as a drug:

- The psycholitic therapy, which involved the fragmented administration of low doses of LSD togheter with psychoanalysis
- The psychedelic therapy, which involved a single administration of a high dose of LSD within a psychotherapeutic session

The highly entheogenic features of LSD, togheter with the pleasantness of the induced hallucinations, quickly transformed it in a recreational substance, which was banned due to its enormous diffusion, especially among young people (Agnese Codignola, 2018).

Nowadays, LSD is the subject of numerous researches, precisely for its properties as a psychedelic, a term coined in 1956 by Humphry Osmond whose etymology indicates a substance capable of "manifesting the psyche".

In 2016 Carhart-Harris recruits twenty healthy people and administers 75 micrograms of LSD or placebo into a vein, measuring the Resting State Functional Connectivity (RSFC) by

magnetoencephalography (MEG) and functional magnetic resonance imaging (fMR), the oxygen contnent of the blood by the BOLD-contrast imaging and the cerebral blood flow (CBF)(Robin L. Carhart-Harris, 2016).

This paper shows three important results:

- The first is that LSD binds to the serotonin receptors 5HT-2A, highly expressed in brain areas involved in cognitive functions and in the visual cortex (V1)
- The second is the neuroscientific explanation of hallucinations: neurons of the visual cortex, which usally have very limited pathways and stimulate only small cortical areas involed in images' processing, under the effect of LSD are capable to stimulate the whole brain, offloading inputs to other nerve cells that have never received and reacted to visual information
- The third is that LSD constrict the veins of the brain and so the cerebral blood flow is reduced in some areas (e.g. the DMN, see next session) and enhanced in others (Figure 1)

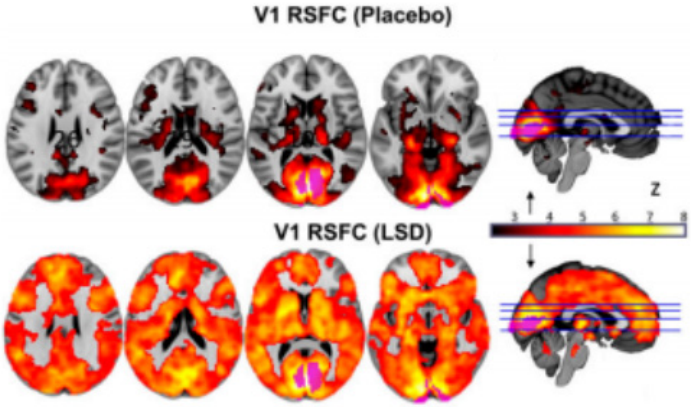

Figure 1: Significant between-condition differences (orange=increases) in RSFC between the V1 seed region (purple) and the rest of the brain

THE ROLE OF NITRIC OXIDE IN LSD HALLUCINATIONS AND PSYCHOSIS

A hierarchical organization exists in the brain: there is a main system called Default Mode Network (DMN), with the function of command, supervision and coordination center, with the aim of integrating and ordering the large traffic of information always present (Agnese Codignola, 2018) The DMN includes areas of the thalamus, of the posterior cingulate cortex and of the medial prefrontal cortex which consists to a significant extent of serotonergic neurons, whose oscillatory and synchronized activation always has an inhibitory effect, since the brain has to make thousands of choices every second and cannot simultaneously take into account all the stimuli that bombard it.

LSD, binding to serotonin receptors of the DMN, prevents the serotonin to bind, temporarily abolishing the hierarchical organization of the brain.

The DMN can represent the Ego, conceived as a mechanism of coercion, superimposed on the rest of the brain and conditioned starting from childhood, which decides what can reach consciousness and what must be removed (Richard Louis Miller, 2017).

The brain in physiological conditions uses well-established neural conduction patterns formed through different learning modalities. These ones can be considered as software which makes use of a neural connection hardware whose computing potential is much higher than that required by the physiological conditions of the brain. Under the effect of LSD, new neural connections appear, exploiting the great potential of the neural networks when they are not interconnected by the physiological patterns of neural firing.

This process can lead to the dissolution of pathological neural circuits that underlie many mental pathologies: in thie way LSD is capable to "reset" the brain, which turns into a blank slate capable of learning new patterns that can replace the pathological ones (Agnese Codignola, 2018). For this reason LSD is now studied as a psychiatric drug which could be available very soon for clinical purposes.

The effect of LSD is due to the fact that, as all the psychedelics in general, it reduces the blood supply to the DMN regions, allowing the entire brain to communicate in a new and physiologically anarchic way. Since the main regulator molecule of the cerebral blood vessels is Nitric Oxide (NO) (Edelman and Gally, 1992, Philippu, 2016), I claim that this molecule is highly involved in the process. In particular where the veins constrict, there's a lack of NO.

On the other hand, in other brain regions the blood flow increases, due to an increased concentration of NO, and with more blood, more oxygen and glucose are available, so that the neural cells can interact more energetically and chaotically, causing the sensation of consciousness expansion typical of the psychedelic experience (Richard Louis Miller, 2017).

Since LSD hallucinations are very similar to clinical psychosis, I speculate for the first time that this also could be the pathophysiological mechanism beneath of such a mysterious pathological condition. My statement can be supported by evidences of the abnormalities of Nitric Oxide concentration in the schizophrenic brain (I. Das et al. 1996, I. Das et al.1995, Akbarian S et.al, 1993, Vinuela A et al., 1933, Hans-Gert Bernstein et al. 2005).

Auditory verbal hallucinations (AVHs), i.e. "to hear the voices" in jargon, are a typical psychotic symptom associated with deficits in auditory and speech-related networks. Has been shown that this condition is caused by an increased CBF in the auditory and striatal areas and a reduced CBF in the visual and parietal areas: this suggests that there exists a CBF redistribution asso-

ciated with AVHs (Zhuo et al., 2017). I claim that the molecule that determines this altered (with respect to the physiological) CBF redistribution is Nitric Oxide.

Another fact that supports my theory is that in shizophrenics the restingstate cerebral blood flow (rCBF) is significantly increased in the striatum and decreased in the prefrontal cortex: this fact is correlated to the findings that LSD enhances the connectivity of certain brain areas due to an incresed CBF, and silences other areas reducing their CBF, infact the increased striatal rCBF determines an increased striatal dopaminergic activity, while a decresed rCBF in the prefrontal cortex implies a decreased prefrontal functioning (Kindler et al., 2018).

Plus, althought is well now that the main neurotransmitter involved in psychosis is dopamine; Nitric Oxide is capable to influence the dopaminergic neurotransmission and has been shown that the dopaminergic abnormalities found in psychotic disorders may be secondary to Nitric Oxide dysfunction (De Oliveira et al., 2016).

REFERENCES

1. Albert Hofmann(2015): LSD-Il mio bambino difficile. Ed. Feltrinelli
2. Agnese Codignola(2018): LSD-Storia di una sostanza stupefacente, Parte Prima: da farmaco a droga. Ed. UTET
3. Agnese Codignola (2018): LSD-Storia di una sostanza stupefacente, Parte Seconda: da droga a farmaco. Ed. UTET
4. Robin L, Carhart-Harris (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. PNAS first published April 11.
5. Richard Louis Miller(2017). Psychedelic Medicine. Park Street Press
6. Edelman, Gally (1992). Nitric Oxide: Linking space and time in Brain,Proc. Natl. Acad. Sci. USA. 89:11651-11652
7. Philippu (2016). Nitric Oxide: A Universal Modulator of Brain Function
8. I Das (1996). Elevated endogenous nitric oxide synthase inhibitor in schizophrenic plasma may reflect abnormalities in brain nitric oxide production. Neuroscience Letters. 215:209-211
9. I Das (1995). Elevated platelet calcium and nitric oxide synthase activity may reflect abnormalities in schizophrenic brain. Biochem. Biophys. Res. Commun. 212:375-80
10. Akbarian S, Bunney Jr. WE, Potkin SG, Wigal SB, Hagman JO, Sandman CA, Jones EG (1993). Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Archives of General Psychiatry. 50:169-77
11. Akbarian S, Vinuela A, Kim JJ, Potkin SG, Bunney Jr. WE, Jones EG (1933). Distorted distribution of nicotinamideadenine dinucleotide phosphatediaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Archives of General Psychiatry 1993b;50:178-87
12. Hans-Gert B, Bernhard B, Gerburg K (2005). The many faces of nitric oxide in schizophrenia. A review. Schizophrenia Research 78:69-86
13. Zhuo (2017). Cerebral blood flow alterations specific to auditory verbal hallucinations in schizophrenia. 210:209-215
14. Kindler (2018). Increased Striatal and Reduced Prefrontal Cerebral Blood Flow in Clinical High Risk for Psychosis. Schizophrenia Bulletin. 44(1):182-192.
15. De Oliveira (2016). Nitric Oxide's Involvement in the Spectrum of Psychotic Disorders. Curr Med Chem. 23(24):2680-2691.