Mechanisms of LSD: a Glimpse into the Serotonergic System

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In 1938, Albert Hoffman discovered, invented a substance that would revolutionize the American drug culture forever and would change how we, as psychologists and biologists, thought about psychosis. That substance was LSD. A simple molecule, LSD has the potency that no other drug has. Only a drop will produce the desired hallucinations and euphoria. In addition, it does not seem to be physically addicting, although tolerance to the drug can develop in as few as three days but disappears after week of abstinence. Much 'research' has been done into the actual effects of the drug. LSD most profound effect on behavior is the production of sensory distortions, such as hallucinations, and euphoria. It also produces dilated pupils, increased blood pressure, and increased heart rate (7, 9). However, little is know about the mechanisms by which it acts. It is known that LSD affects the serotonergic system in the brain. However, the actual ways in which it acts on that system to modify behavior remains unclear. Before we explore the current research into LSD, it may be helpful to review some of the ways in which serotonin affects behavior. Serotonin (also called 5-HT) is a neurotransmitter that is produced from tryptophan. Although serotonin is only produced by a small number of neurons (1000's), each of those neurons innervates as many as 500,000 other neurons (3,12). For the most part, these neurons originate in the Locus Coerleus (LC) and the Raphe Nuclei (RN) (12). The LC controls the release of norepinephrine, a neurotransmitter/hormone that regulates the sympathetic NS. It also has neurons that extend into the cerebellum, thalamus, hypothalamus, cerebral cortex, and hippocampus (12). The RN extends its projections into the brainstem and up into the brain (12). It has been suggested that neurons in this region of the brain may be responsible for the inhibition of sensation, thus "protecting the brain from sensory overload." (12) The fact that these two regions innervate virtually every part of the brain shows that serotonin can activate large portions of the brain from a relatively small area of origination. Serotonin seems to have an inhibitory effect on these neurons (1, 12). Thus, it would decrease the occurrence and frequency of action potentials in the neurons that it innervates. Because of this, it produces neural activity (of lack of activity) that are in some way an inhibition of behavior. Sleep is the most obvious example of this. Decreases in serotonin levels in the brain have been linked to a delayed onset of sleep (2). Serotonin may encourage the lowering of physiological activity in the body that is associated with the onset of sleep. Aggression is also related to serotonin levels in the nervous system. Suppression of aggression can be thought of as the suppression of activity and thus an inhibitory action. Patients who show increased aggression, also have low levels of serotonin. Depression is an illness that also seems to have one of its causes in low serotonin levels (2,3). Many of the anti-depressants currently on the market are drugs that work by increasing serotonin levels in synapses. However, given that serotonin is an inhibitory neuron, and depression appears to be mostly a decrease in behavior and affect, one would expect that depression would be caused by an increase in serotonin levels, rather than a decrease. However, the serotonergic system of the nervous system is a complex system that mediates so many behaviors, it may have multiple functions that the scientific community has only an inkling of. Some of these functions are revealed by the effects of LSD.

As with depression, the action of LSD is not completely understood. There is evidence, however, that serotonergic neurons are involved. LSD is structurally similar to serotonin and seems to affect many of the systems that serotonin has been implicated in (12). In addition, administration of haloperidol blocks the hallucinations associated with LSD use (7). Haloperidol has an especially strong affinity for serotonin receptors. Also, other psychedelics that have similar effects to LSD have been shown to affect serotonin producing neurons. MDMA, or ecstasy, blocks the reuptake of serotonin, thereby leaving more serotonin in the synapse and prolonging activation (6). Prolonged use of MDMA results in destruction of serotonergic neurons in the brain (4,5). Because of the similarities between ecstasy 'trips' and LSD 'trips,' it can be concluded that they must activate a similar pathway, i.e. the serotonergic pathway. Several theories of the mechanism of LSD have been postulated. Each one presents a way in which LSD could affect behavior through activation of serotonergic neurons along with research to support it. However, each one has its weaknesses. In the end, it is difficult to determine how LSD actually alters behavior. The first theory is that LSD is a serotonin antagonist, specifically activating (or actually blocking) 5-HT2 receptors (12). This would prevent serotonin from having its normal effect. Support for this theory comes from studies that have shown that administration of some 5-HT2 antagonists do not decrease the effects of LSD, as you would expect if LSD was a serotonin agonist. Activation of 5-HT2 receptors seems to cause serotonin to have an excitatory effect on some neurons. LSD prevents this action, thus having an antagonistic effect on the 5-HT2 serotonin system (12). However, even within this theory there are problems. The general theory of LSD as an antagonist is consistent with how it affects behavior. LSD seems to increase sensation, heart rate, and blood pressure, all of which are excitations of the nervous system. Because serotonin is an inhibitory neurotransmitter, antagonism of serotonin would result in an increase in neural activity. However, the fact that LSD is an antagonist to 5-HT2 receptors specifically makes this conclusion problematic. Because of the special action of 5-HT2 receptors, antagonism of serotonin at those receptors would result in a decrease in neural activity which would not explain the effects of LSD. If 5-HT2 receptors are in fact excitatory, one would expect antagonism of this system to have an inhibitory effect. The next theory postulates that LSD is in fact a 5-HT agonist rather than an antagonist (12). One researcher was able to train rats to discriminate between LSD and saline based on it psychological effects. When the rats were given certain 5-HT2 antagonists, the rats lost the ability to discriminate between the two (12). Also, LSD has been shown to have a higher affinity for 5-HT receptors over all than serotonin but has a lower potency (12). Thus, while is more likely to bind to the receptors, it is not as likely to have an effect as serotonin. Even though LSD has some activity, it does not appear to be very strong. LSD may appear to be an antagonist even though by definition it is an agonist. The last theory partially combines the last two theories. This theory postulates that 5-HT1 and 5-HT2 have an agonist/antagonist relationship. Thus substances that are agonistic to 5-HT1 receptors are antagonistic to 5-HT2

receptors (8). This is supported by the above research. LSD operates under this mechanism by enhancing serotonin activity at 5-HT1 receptors, while also blocking 5-HT2 receptors from the more effective activation of serotonin.

The interesting point of this theory is its implications for the actual effects of those two serotonergic systems. Agonization of the 5-HT1 receptors by LSD indicate that they might be involved in the production of moods. If low serotonin produces a decrease in positive moods, as in depression, then agonization of serotonin levels should produce a more positive mood state. LSD agonization would be consistent with the production of euphoria and mood changes that are associated with LSD use. The 5-HT2 receptors might then be responsible for the control of sensation and possibly autonomic nervous system control. Under the control of LSD, sensation appears uninhibited. Users report enhanced sensations, synesthesia, and distortions of sensations. All of this would seem to be a result of over activation of the sensory system. In addition, LSD produces an increase in heart rate, blood pressure, and body temperature, all of which are a result of activation of the sympathetic nervous system. Because it has been shown that LSD limits serotonin's activation of the 5-HT2 receptors, it can be concluded that these receptors must be involved in the inhibition of sensation and the sympathetic branch of the autonomic nervous system under normal conditions. The only problem with this theory is that it fails to reconcile the theory that 5-HT2 receptors are actually excitatory.

Once again, the nervous system proves to be too mysterious for explanation. As with most alterations of behavior, researchers can explain what happens but not how it happens. Our postulated theories of LSD action only allow us a glimpse at the whole picture, and it is a rather incomplete, confusing glimpse at that. We can guess how LSD affects serotonin levels, but there will always be evidence that contradicts the theories. There will always be a part of the brain that uses serotonin in a different way than the other parts, a receptor that activates neurons differently. The only way that we can get at the truth is to approach the problem from different angles. One approach to the problem of LSD action would be to investigate where the different 5-HT receptors are located in the brain. Location may shed light on the actual purpose of these receptors. Based on the theories and experiments described above, one might assume that 5-HT1 would be located in areas of the brain responsible for the production of mood. Such areas might include the frontal cortex and the hypothalamus. 5-HT2 receptors might appear in the lower regions of the brain that are devoted to the production of basic physiological functions as well as in areas devoted to sensation and the interpretation of sensation. An interesting point is the fact that in the end, LSD does not seem to have an inhibitory effect on the areas involved with the I-function (where ever they may be). LSD users are always aware that the hallucinations and euphoria are a product of the substance; the awareness is called insight (7). This may be the most important implication for the serotonergic system. Because LSD is unable to produce alterations in the I-function, serotonin appears not to be involved in the production of the sense of self, an interesting point considering the fact that it effects almost every other facet of behavior.

References

(1) A series of pages on serotonin

(2) Class homepage at the California State University at Chico

(3)Class papers for Lafayette University

(4) National Institute for Drug Addiction

(5) National Institute for Drug Addiction

(6) http://www.paranoia.com/drugs/mdma/mdma.ssri

(7) Virtual Hospital

(8) Term paper posted by Ian Leicht

(9) http://www.addictions.org/lsd.htm

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