

# Study of LSD pathway through drug discrimination in rats

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## **Abstract**

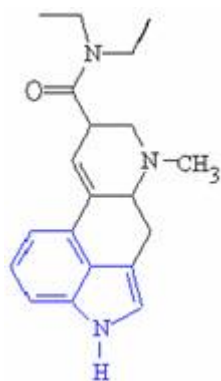
Researchers have long been interested in identifying the general pathway of psychosis induced by psychedelic hallucinogens such as lysergic acid diethylamide (LSD), as it not only sheds light on the neuronal correlates of various perceptual and cognitive processes, but also leads to important understanding about the underlying psychophysiology of psychiatric disorders such as schizophrenia. Furthermore, this knowledge would prove useful in treating substance abuse and addiction. In the proposed study, the psychoactive aspects of the effects induced by LSD and their possible corresponding neuronal pathways will be examined in trained rats through two-lever drug discrimination tasks. As confirmed in past studies, LSD activates both serotonergic and dopaminergic systems, and it has been postulated that possible interaction between the two systems play a dominant role in inducing the perceptual and cognitive alterations experienced under the influence of LSD. The proposed project will assess the degree of this interaction with respect to altered signaling of serotonin 5-HT(2A) receptors and dopamine 2D receptors via the use of antipsychotic agents, which suppress different effects of LSD. Various antipsychotics, such as piperperone, haloperidol, and risperidone, will be applied as discriminative thresholds are obtained and compared accordingly. The target specificities of the agents will help elucidate the roles of the serotonergic and dopaminergic systems in generating the various psychoactive properties involved.

## **Background and Significance**

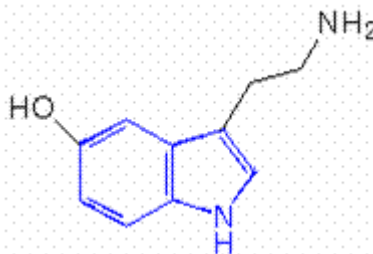
Since the unexpected discovery of lysergic acid diethylamide (LSD) by Albert Hoffman in 1938, much research has been put into unraveling the mechanisms of the psychoactive properties of the drug. It is extremely potent, acting on scales of micrograms, yet it has shown to cause profound effects on human behavior, such as hallucinations, euphoria, and changes on other cognitive processes. It has long been demonstrated that it not only alters and distorts the transmission of sensory impulses along various sensory pathways to the brain, but also produces certain somatic effects through the autonomic nervous system, resulting in dilated pupils, increased blood pressure, and increased heart rate. However, though much groundwork has been established about the nature of the drug, the exact mechanisms of LSD remain largely unexplained.

LSD is structurally similar to serotonin (5-HT), which is an important neurotransmitter that innervates almost all regions of the brain. LSD has been shown to have high affinities for 5-HT receptors, most importantly 5-HT(2A) receptors, which

have long been suspected to be the main source of hallucinogenic effects attributable to LSD. Serotonergic neurons are mainly clustered around the raphe nuclei, located in the middle of the brainstem from midbrain to the medulla. Postsynaptic 5-HT receptors in the visual regions have been believed to be inhibitory, which seemingly indicates that an interruption of serotonin activity would lead to excitation of various sensory modalities [1]. However, recent studies seem to indicate that LSD serves as a partial agonist on 5-HT receptors rather than an antagonist.



LSD



serotonin

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[http://www.chemsoc.org/exemplar/chem/entries/2004/bristol\\_rosling/My%20Webs/LSD.HTM](http://www.chemsoc.org/exemplar/chem/entries/2004/bristol_rosling/My%20Webs/LSD.HTM)

Although traditionally the hallucinogenic effects of LSD have mainly been attributed to serotonin, recent studies reveal that LSD also activates the dopamine system, which seems to contribute significantly to the psychoactive properties as well [2]. Researches have shown that LSD has a specific effect on D2 dopaminergic receptors. It has been speculated that the resulting psychotomimetic effects are due to complex interaction between serotonin and dopamine systems.

The proposed project will attempt to explain the dominant mechanisms of LSD. Due to today's legal regulations, experiments on human subjects would be almost impossible to conduct, and recent studies on LSD have been conducted mainly on laboratory animals such as rats. It is of course impossible to directly probe into the minds of the animals or communicate with them in a straightforward manner to understand their subjective experiences, but behavioral training based on conditioning can help reveal their state of mind. The proposed project will address a few specific questions related to the mechanisms of LSD. 1) To what extent does the serotonergic system have an effect on the interoceptive experience in LSD-administered subjects? 2) To what extent does the dopaminergic system have an effect in the interoceptive experience in LSD-administered subjects? 3) Is it the interaction of the two systems that give rise to the hallucinogenic and psychoactive properties? If so, to what extent do the two systems interact to allow such properties to take place? 4) Alternatively, though past research has mainly focused on the serotonin and dopamine systems and postulated their dominance in inducing psychotomimetic effects, perhaps a different route is to be pursued. As LSD also influences many other systems, such as the noradrenergic system and glutamate transmission, it is possible that one of these systems plays a more critical role than traditionally believed.

This study will investigate the different neuronal systems activated by LSD in a systematic manner and provide some important insights into the experienced perceptual and cognitive changes on a neuronal and chemical level. Because the many of the psychoactive effects induced by LSD are vastly similar to the symptoms of psychiatric disorders such as schizophrenia, scientists have long been drawing parallels between the two and trying to study the nature of cognitive deficits associated with schizophrenia through drug models. The outcome of the proposed project will hopefully provide practical applications that can be generalized to help with the development of treatment for schizophrenia. In addition, the findings can also be extended to gain better understanding about the mechanisms of drug abuse and addiction.

### **Specific Aims**

The proposed experiment will assess the degree of participation of the serotonergic system and dopaminergic system in inducing the psychoactive properties of LSD in rats in a quantitative manner. It also intends to investigate how the interaction of the two systems influences the interoceptive effects of LSD.

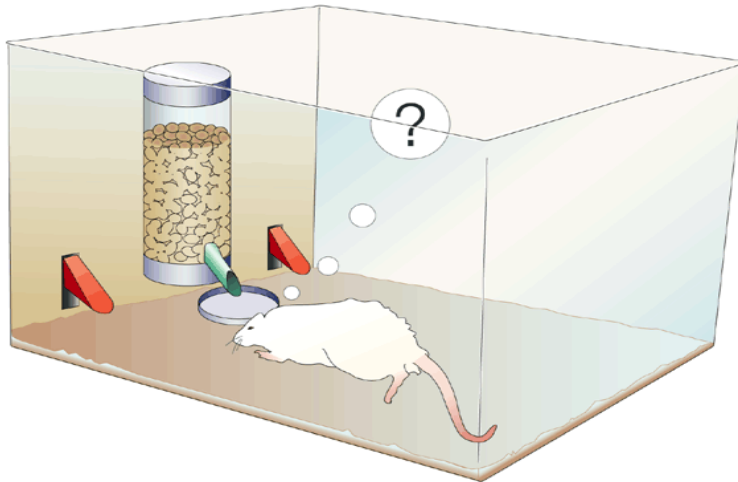
### **Methods**

This proposed study will attempt to demystify the dominant mechanisms of LSD through a behavior approach in rats. Drug discrimination tasks[3,4] have been widely used as an *in vivo* model in measuring the ability of animals to discriminate between subjective experiences induced by similar or different pharmaceuticals. In the proposed project, we will attempt to establish a behavioral model to examine how the stimulus properties of LSD are related to altered signaling of serotonin receptors and dopamine receptors.

#### *Initial training*

The rat will receive a daily training session of 20 minutes in a specially designed box, which allows dispense of food pellets when the rat correctly presses one of the two levers ten times. Eventually, when the rat acquires the skill of pressing a lever for food, drug discrimination training will begin. In each daily session, 30 minutes before it is placed in the box, the rat will either receive an injection of LSD (0.12 mg/kg) or saline. When LSD is injected, the rat will have to press the right lever ten times in order receive food pellets from the dispenser. When saline is injected, the rat will have to press the left lever ten times to be rewarded food. LSD and saline injection sessions will alternate in a random manner, until the rat learns to press the right lever when LSD is injected and the left lever when saline is injected. The rat will have learned to discriminate LSD based on its interoceptive properties.

Past experiments show that a rat trained in this manner will press the lever for LSD upon receiving an agent that produces sufficiently similar interoceptive effects. Otherwise, the rat will press the lever for saline even when other interoceptive effects are produced. [3]



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[http://www.nature.com/cgi-taf/DynaPage.taf?file=/nrd/journal/v2/n4/full/nrd1062\\_fs.html](http://www.nature.com/cgi-taf/DynaPage.taf?file=/nrd/journal/v2/n4/full/nrd1062_fs.html)

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#### *Testing the effects of serotonin system activation*

Pirenperone, a 5-HT(2A) antagonist [5], will be injected in varying doses after injection of LSD during the test sessions. The hungry rat will then be placed in the box. If it chooses to press the right lever, it means that the antagonistic effect is too minimal to initiate any detection in interoceptive experience. The experiment will proceed in this manner until a discriminative response is observed. This would represent a threshold dosage of pirenperone in effecting perceptual differences in rats, which would allow an assessment of the role of 5-HT(2A) receptor signaling in a quantitative manner. Other 5-HT(2A) antagonists could also be tested in this manner.

#### *Testing the effects of dopamine system activation*

Haloperidol, a D2 antagonist, will be injected in varying doses after injection of LSD during the test sessions. The rat will be placed in the box and left to press a lever. This would yield a threshold dosage of haloperidol in altering the perceived interoceptive state in rats through the discrimination task, which would help assess the role of D2 receptor signaling and dopamine activation in a quantitative manner. Other dopamine antagonists could also be tested in this manner.

#### *Testing the effects of the interaction of multiple systems through other antipsychotics [6]*

Risperidone, a potent antipsychotic that has been tested in the past to antagonize LSD effectively, acts on both 5-HT(2A) receptors and D2 receptors. It is used here to measure the interoceptive discrimination threshold perceived by rats as well as serve a comparison for the dopamine- and serotonin-only tests. It will be administered to the rats in varying doses after injection of LSD during the test sessions, similar to the parts described above, and the experiment will proceed in a similar manner.

Each section of the experiment will be repeated to ensure that the data are reproducible. From literature, the amount of deactivation of the serotonergic and dopaminergic systems associated with pirenperone and haloperidol respectively will be

matched accordingly with the quantities applied for the rat to experience an interoceptive difference. These data will be compared to the results obtained from the risperidone test. This will reveal the amount of deactivation of each system needed to initiate a perceptual discrimination, which in turn will demonstrate the role each system plays in the mechanisms of LSD.

There are several potential problems and pitfalls involved with the experiment. First of all, there might be other systems that may play critical roles in affecting LSD mechanisms that can possibly confound the results, because there might be unforeseen interactions between those systems and the serotonergic and dopaminergic ones described. Secondly, although the antipsychotic agents suggested above have primary effects in the described receptors, they also serve as antagonists on other neurotransmitter receptors in varying degrees. This problem can be subdued by exploring other possible antipsychotics that possess better specificity in the targeted receptors. Furthermore, the amount of tolerance the rats might develop towards LSD can possibly confound the data. Similarly, extinction of conditioning can also skew the data in the other direction. This would require an intricate balance in duration between consecutive administrations of the drug.

### **Future Direction**

It will be worth investigating how other systems besides the serotonergic and dopaminergic ones balance in the equation of psychoactive properties of LSD. It has been postulated that enhanced glutamate release in the prefrontal cortex play an important role modulating the alteration in cognitive processes during psychosis induced by LSD. However, some research has shown that increased glutamate levels is a downstream effect of 5-HT<sub>2A</sub> receptor activation [7, 8]. In addition, it is possible that LSD not only acts on the receptor signaling of the serotonergic and dopaminergic systems, but also modulates the downstream transmission of serotonin and dopamine. How this can compound the psychoactive effects is a matter that should be pursued further.

It is also important to extend the research to primates in order to understand the effects of LSD-induced psychosis in humans more effectively. Such studies would be much more time and resource consuming, but would allow more direct methods such as fMRI imaging to gain better insights into the neuroanatomical sites involved in altered states of consciousness induced by hallucinogens.

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