The Efficacy of Model Organisms for Hallucinogen Research

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Introduction

In the 1830s, Charles Darwin set out for a journey to the Galapagos Islands that would forever shake the foundations of how humans view the world around them. During his travels across the Galapagos islands, Charles was intrigued by the claims that similar animals that lived on different islands apparently had different morphologies. The two organisms he studied were the Galapagos tortoises and the more famously known finches, also known as Darwin's finches. Contrary to popular belief, Darwin did not make the initial connection between the physical characteristics of these finches and their role in natural selection during his journey. It was not until a year after his departure from the Galapagos islands that Darwin finally associated the finches with his new theory of evolution through natural selection (Sulloway 1984).

Critical of Darwin's groundbreaking claims, a lone Austrian friar by the name of Gregor Mendel would also go on to leave his mark on the evolutionary sciences. Mendel's experiments into heredity and hybridity using pea plants was one of the first cases of the use of a model organism for modern research purposes. In his published work, Mendel described the importance of using an organism that gives consistent, reliable, and relatable results, something that still rings true over 150 years after his revolutionary experiment (Muller 2010). In modern times, model organisms are used in researching everything from social behavior to rare genetic diseases, but a relatively new class of drugs, hallucinogens, have proposed an interesting conundrum. Hallucinogens are very well known for their ability to induce altered states of consciousness, some of which include altered perceptions of time and spiritual awareness, and as their name suggests, hallucinations. Together, these subjective phenomena question whether or not the model organisms that are used today are effective for researching hallucinogenic drugs.

What Makes a Good Model Organism?

Before commenting on the efficacy of model organisms in the research of hallucinogens, it is important to consider what makes a good model. Some of the marks of a valuable model organism include its ease of use, availability, and that the research done with said organism can be correlated with similar biological or behavioral processes within other organisms. As in many discoveries in science, finding an effective model organism is a matter of random chance and trial and error. For example, while being viewed as a model early in the 20th century, Arabidopsis did not gain popularity until the 1980s when scientists discovered its simple and easy to manipulate genome, short life cycle, while still having the complexities inherent to flowering plants (Muller 2010). Conversely, the guinea pig, originally ideal with its short life cycle lost much of its popularity when it was found to have a difficult genome to work with and manipulate. The colloquial term, "to be a guinea pig" still remains in use today as evidence of its prior popularity (Crow, 2002; Muller 2010).

One of the most well known, and studied, model organisms for biological research are yeasts, specifically Saccharomyces cerevisiae. Its efficacy as a model organism can be attributed to its conserved genome, which it shares with many other organisms including humans, remarkably short life cycle, and the ease by which researchers can manipulate its genes (Botstein 2011). When S. cerevisiae's genome was originally mapped out, researchers noted how similar, or conserved, it was to the human genome. Not only were the DNA sequences nearly identical, the proteins and their associated functions were also found to be similar to many eukaryotic organisms, making any research done on S. cerevisiae nearly universally applicable (Botstein 2011). Its short life cycle has also been an advantage for scientists because of the ease of creating and isolating mutant yeasts, and for long term evolutionary research (Botstein 2011). In short, yeast is an example of an effective model organism in biological research.

While yeasts are effective in studying how altering genomic sequences can affect protein interactions, there are some limitations to using yeasts as a model organism, one of which being behavioral research. Despite being recently discovered as a possible animal model, the zebrafish (Danio rerio) has been gaining in popularity for behavioral research. Much of the zebrafish's brain anatomy and circuitry are homologous to those in humans, including those relating to reward behavior, spatial learning ability, aggression, and anxiety (Norton 2010). Additionally, zebrafish have been used to study behavioral genetics and the effects of addictive substances such as nicotine and ethanol (Norton 2010). Currently, zebrafish remain one of the only genetic models for effectively studying appendage and heart regeneration (Muller 2010).

Despite serving as a decent approximation of behavior in humans, the results of studies done with animal models of behavior are often difficult to correlate with humans directly. One example of the ambiguity that can exist between correlating animal results to humans is that of alcohol and its addictive effect. Like many other behavioral research, much of the studies that focus on alcohol addiction use popular model organisms like dogs, rabbits, rats, cats, fish, and primates (Ankeny 2014). In many of these experiments, the animals are introduced to alcohol and then observed to see if they prefer to drink water or more alcohol. Unlike humans, researchers found that the animals did not develop any signs of alcoholism. Even those that did drink a large amount of alcohol, it was not enough to considerably raise their blood alcohol level (Ankeny 2014). Additionally, the environment that humans consume alcohol is much different than that of a rat inside a controlled cage in a laboratory. Drinking is heavily associated with social situations and, without those settings or the ability to socially interact at a human level, much of these studies failed to correlate with human behavior.

Model Organisms for Hallucinogen Research

Despite being unique somewhat in their effects in living organisms, many of the animal models that are used for other areas of study are also used for researching the effects of hallucinogens. Many of the models used for hallucinogen research are animals, not microscopic organisms, in order to try and connect the physiological effects of the psychotropic compounds and the behavioral effects that they cause. In a study done by Halberstadt et al in 2013, they used a mouse model to see the behavioral effects of four hallucinogens: LSD, DOI, and SKF38393. Their method of measuring the effects of the hallucinogen was through the head twitch response (HTR) which is associated with the 5-HT2A pathway, a common receptor site for most hallucinogens. While originally being more of a subjective measurement, Halberstadt et al quantified the HTR by using a magnetometer and a magnet attached to the head of the mice, allowing for more accurate measurements for 5-HT2A activation.

In another study done by Nichols et al in 2002, they studied the effects of hallucinogens in a different animal model with a different method. Nichols et al tried to connect the changes in visual processing and locomotor activity that happen under hallucinogenic drugs in humans, to Drosophila flies. Like Halberstadt et al, they focused on the 5-HT2A pathway and used varying dosages of LSD and an inhibitor to the 5-HT2A receptor. They found that there was a marked decrease in the locomotor ability, less spontaneous actions, and visual processing capability, inability to follow a cue, making Drosophila a promising candidate for behavioral research with hallucinogens.

For many hallucinogen experiments studying the behavioral effects on animal models, one of the key things researchers look for are behaviors that do not otherwise show up when the animal is not under the influence. In a classic study done by Jacobs et al in 1977, they wanted to test the validity of cats as a behavioral model for LSD research. After administering LSD to a set of cats, they noticed four behaviors that happened either at an increased frequency than normal or was completely absent when the cats were given saline. Instances of limb flicking and investigatory behavior significantly increased, and abortive grooming appeared with the addition of LSD. Abortive grooming can be described as when the cat moves to clean itself with its tongue and either fails to open its mouth or begins to lick nothing (Jacobs 1977). The last behavior is the most important, but hardest to measure, hallucinogenic behavior. Some cats were seen jumping or attacking nothing, a behavior not seen in untreated cats. In the end the researchers found that the cat is an effective animal for modeling behavior under the effects of LSD because of the reliability of measuring the first three behaviors, but not hallucinogenic behavior.

Advances in Research with Hallucinogens

Over the past several decades, animal models have shown to be valuable source of information when researching the physiological mechanisms of hallucinogens. In 2007, Gonzalez-Maeso et al tried to pinpoint what exactly is occurring in the 5-HT2A pathway when a hallucinogenic compound binds to the receptor instead of one that is not psychotropic. Based on previous studies done on hallucinogenic compounds, it is widely known that the 5-HT2A pathway is required for the psychoactive effects of hallucinogens, but what they did not know was why some compounds that acted as 5-HT2A receptor (2AR) agonists did not produce hallucinogenic effects (Gonzales-Maeso 2007). Using mice as their model organism, they administered LSD and observed the resulting signaling 5-HT2A pathways, using patch clamps, transcript changes via FISH analysis, among other methods. They concluded that even though may act on the same 2AR receptor, they can result in different signaling pathways which are responsible for the difference in behavior seen when one introduced to a hallucinogenic compound.

Much like their usefulness in elucidating physiological mechanisms and pathways, model organisms have shown to be important in the research of behavioral changes that hallucinogens can cause. A recent experiment done in 2015 studied the long term effects of ayahuasca use on anxiety and memory in rats. Ayahuasca is unlike other hallucinogens because it a mixture of two different plants, Psychotria viridis and Banisteriopsis caapi. It was originally used in shamanistic rituals indigenous to tribes in South America, but its use has spread to North America and Europe in the last thirty years for recreational and artistic purposes (Favaro 2015). In this study, Favaro et al treated rats with three different dosages of ayahuasca and a control group with just water over thirty days. Over the course of those days, Favaro et al tested the rats' anxiety and memory using an elevated plus maze, Morris water maze, and a conditioning chamber with an electrified floor. Their results showed that rats who were given large amounts of ayahuasca were more susceptible to keeping the learned contextual fear response in the electrified chamber. In short, rats under the long term effect of ayahuasca remembered the stressful memory of being shocked more. However, the author also mentions that despite showing a link between anxiety, memory, and long term ayahuasca use, the results cannot be correlated with human behavior regardless of the similarities present.

One last example of research done with hallucinogens is a study done in 2014 done by Buchborn et al which explored the therapeutic benefits of LSD in rat model for depression. Selective serotonin reuptake inhibitors (SSRIs) are often prescribed as antidepressant drugs and act on the 5-HT receptor family, one of which being 5-HT2A (Celada 2004). For this study Buchborn et al used bulbectomized rats, rats that have had their olfactory bulbs removed, and an avoidance learning task to test for depression linking avoidance learning. The avoidance learning task trained the rats to avoid the shock on an electrified floor after the sound of a buzzer. Without treatment, bulbectomized rats showed significantly decreased reactions to the avoidance learning task when compared to the normal rats. When bulbectomized mice were given LSD, their ability for avoidance learning returned nearly to normal levels, suggesting a rebalance in the 5-HT2 signaling pathway. On a larger scale, these results might help pave the way in understanding how hallucinogens alleviate emotional stresses (Buchborn 2014). Even though research using hallucinogens has been greatly limited since their illegalization in the 1960s, these studies show that there has still been great strides in researching the effects and possible benefits that hallucinogens may provide.

The Uniqueness of Hallucinogens

Despite the usefulness of model organisms in elucidating physiological mechanisms and approximating behavior in humans through animal models, there are still many important traits of hallucinogens that can only be seen in humans. As brought up in the Ankeny et al review done in 2014 regarding the difficulty of linking alcoholism in humans to animal research, there are difficulties in correlating behavioral hallucinogen research as well. Many studies have tried relating pathways, like the 5-HT2A receptor, to behaviors like the head twitch response or limb flicking, but the question remains as to how those behaviors relate, if at all, to human behavior. However, behavioral studies that focus on more relatable processes like memory, anxiety, and learning play an important role in elucidating the possible side effects of consuming hallucinogens.

One of the most prominent aspects of hallucinogens are, as their name suggests, their ability to make a person who takes them hallucinate. In Oliver Sacks' book titled Hallucinations, one of the chapters describes a period in his life when he experimented with many different hallucinogens. In one instance, he took a large dose of morphine and proceeded to be enthralled by the sleeve of his dressing gown that hung on a door in the room. There, he saw thousands of miniature soldiers marching to war against each other, equipped with longbows and shining swords. After coming down from his morphine high, he noticed that this seemingly brief moment lasted twelve hours (Sacks 2013). While amusing to read and imagine, his experience shows how significant the effects a hallucinogenic drug can have on a person. Sacks lost all sense of time and began to see vivid details in his hallucinations, something that would be impossible to measure through conventional model organisms. Even when done in a clinical setting, how is the researcher able to make sense of a hallucination a test subject sees and relate them to physiological pathways?

A study done by Wittmann et al in 2007 attempted to measure the altered perception in time that hallucinogens cause. They gathered twelve volunteers and administered either a high dose of psilocybin, a low dose, or a placebo, and measured the volunteers' ability to press a key at a steady rhythm at different intervals. They found that there was no impairment in the shorter intervals, but once the intervals increased past two seconds, there was a significant decrease in accuracy. There was a decrease in the subjects' ability for anticipatory planning while also noting a subjective change in the passage of time. The results from this study further shows that some aspects of hallucinogens cannot be studied in model organisms, but instead are limited to human trials.

One last aspect of hallucinogens that limits its ability to be studied in model organisms is the strong influence that social settings have on hallucinogens, including their ability to induce higher states of consciousness or promote healing. Even though the matters of consciousness and spiritual healing may be beyond the realm of biological and behavioral sciences, they are nonetheless important in determining the effects of hallucinogens. Hallucinogens have historically been used across many cultures across the world, one of which being the native tribes of Central America and their use of peyote (Jones 2008). The tribes use the peyote cactus not for recreational use, but for heal the imbalances within their life, be they spiritual, physical, mental, or social. The mescaline within the peyote cactus is thought to allow access to different cognitive structures and mechanisms in the brain that result in an increase personal awareness and expanded consciousness (Jones 2008).

Conclusion

While hallucinogens might have unique properties that can only be studied in humans, model organisms can still provide valuable insight into the mechanisms behind how hallucinogens work. Before researching the more fantastical and interesting aspects of hallucinogens, such has how and why people hallucinate or why does time seem to pass by quicker while a person is high, it is important to devote time into researching the foundations behind these phenomena. By using model organisms for physiological studies researchers can attempt to explain the basic pathways that psychotropic compounds affect and link them with areas of the brain, increased neurotransmitter levels, and even down to the level of which genes are affected. Through hallucinogen behavior research, scientists can get a better understanding into the possible immediate and long term effects of psychotropic drug exposure, including things like memory, anxiety, and spatial awareness. In the end, model organisms are very effective in the studying the effects of hallucinogens, just not for the aspects that the general public might be interested in hearing about.

References

Ankeny, R. A., S. Leonelli, N. C. Nelson, and E. Ramsden. 2014. Making organisms model human behavior: situated models in North-American alcohol research, since 1950. Sci Context 27(3):485-509.

Botstein, D., and G. R. Fink. 2011. Yeast: An experimental organism for 21st century biology. Genetics 189(3):695-704. DOI: 10.1534/genetics.111.130765.

Buchborn, T., H. Scroder, V. Hollt, and G. Grecksch. 2014. Repeated lysergic acid diethylamide in animal model of depression: normalisation of learning behavior and hippocampal serotonin 5-HT2 signaling. Journal of Psychopharmacology 28(6):545-552.

Celada, P. V. Puig, M. Amargos-Bosch, A. Adell, F. Artigas. 2004. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. J Psychiatry Neurosci. 29(4):252-265.

Crow, J. F. 2002. C. C. little, cancer and inbred mice. Genetics 161(4):1357-1361

Favaro, V. M., M. Yonamine, J. C. K. Soares, M. G. M. Oliveira. 2015. Effects of long term ayahuasca administration on memory and anxiety in rats. PLOS One 10(12):e0145840

Gonzalez-Maeso, J. et al. 2007. Hallucinogens recruit specific cortical 5-HT2A receptor-mediated signaling pathways to affect behavior. Neuron 53:439-452.

Halberstadt, A. L. and M. A. Geyer. 2013. Characterization of the head-twitch response induced by hallucinogens in mice. Psychopharmacology 227:727-739.

Jacobs, B. L., M. E. Trulson, and W. C. Stern. 1977. Behavioral effects of LSD in the cat: Proposal of an animal behavior model for studying the actions of hallucinogenic drugs. Brain Research 132:301-314.

Jones, P. N. 2007. The Native American church, peyote, and health: Expanding consciousness for healing purposes. Contemporary Justice Review 10(4):411-425.

Muller B. and U. Grossniklaus. 2010. Model organisms – A historical perspective. Journal of Proteomics 73(11):2054-2063.

Nichols, C. D., J. Ronesi, W. Pratt, and E. Sanders-Bush. 2002. Hallucinogens and Drosophila: linking serotonin receptor activation to behavior. Neuroscience 115(3):979-984.

Norton, W., and L. Bally-Cuif. 2010. Adult zebrafish as a model organism for behavioural genetics. BMC Neuroscience 11:90. DOI: 10.1186/1471-2202-11-90.

Sacks, O. 2013. Hallucinations. Vintage Books, New York, New York.

Sulloway. F. J.1984. Darwin and the Galapagos. Biological Journal of the Linnean Society 21(1-2):29-59.

Wittmann, M., C. Olivia, F. Hasler, B. R. Cahn, U. Grimberg, P. Spring, D. Hell, H. Flohr, and F. X. Vollenweider. 2007. Effects of psilocybin on time perception and temporal control of behaviour in humans. Journal of Psychopharmacology 21(1):50-64.