The Efficacy of Model Organisms for Hallucinogen Research

Yuri Parasuk
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

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 is that they are not the main focus of hallucinogenic research. Despite being recently discovered as a useful model organism, 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 being a useful tool for the study of hallucinogenic drugs, the effects of hallucinogens in animals can be difficult to measure. 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 psychotrophic. 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 the relevant condition and measured changes by 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 differences in behavior seen when one introduced 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 who 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-HT2A pathway. On a larger scale, these results might help pave the way in understanding how hallucinogens alleviate emotional stress (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 studies, 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 mesalina 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 as 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.

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References


