4. Why Study Hallucinogenic Drugs in Animals?

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Introduction

What can we learn from studies of hallucinogenic drugs in animals? The Church of Scientology has labelled such studies funded by the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH) as worthless wastes of the taxpayers' money. This year, the Council for Citizens Against Government Waste has joined in the fight against the Federal funding of such research, singling out a 25 year study of hallucinogen mechanisms in animals, supported by NIMH, as being particularly wasteful. In years past, my research grant from NIDA supporting behavioral studies of hallucinogens in rats has been targeted by animal rights activists, including a candle-light vigil protesting a study of 102 rats given phencyclidine. Nevertheless, I and many other scientists believe that we can learn important information from basic studies of hallucinogen action in animal models and that this information may lead to the alleviation of human sufferring. The present essay will illustrate how such benefits may be realized. From the outset, it should be acknowledged that there are many reasons one might wish to understand the mechanisms responsible for the fascinating and often profound effects of hallucinogens. Many believe that exploring the effects of hallucinogens has the potential to teach us important lessons regarding the nature of consciousness and the way it relates to the brain. Here, the focus is specifically on the possible applications of such an understanding to the treatment of mental illness, a more limited but still important domain.

Antipsychotic Medications

Some 40 years ago, the advent of antipsychotic medications that helped treat patients with schizophrenia led to a revolution in our mental health care system. Due in large part to the effectiveness of these medications in many patients, the longstanding practice of institutionalizing schizophrenia patients for their lifetime in state-run mental hospitals gradually came to an end. Indeed, few of these state mental hospitals remain today. Nevertheless, these medications are not without unfortunate serious side-effects and are not effective in treating all schizophrenia patients. Schizophrenia has long been thought to include a group of disorders having different etiologies and requiring different treatments for different patients. Virtually all of our current array of antipsychotic drugs, however, work via a common mechanism of blocking receptors for the neurotransmitter dopamine. Dopamine is the neurotransmitter that is believed to mediate the behavioral actions of drugs such as amphetamine and cocaine. Despite the fact that very little evidence exists for a causal abnormality in dopamine systems in the brains of schizophrenia patients, the vast majority of these patients are treated currently with dopamine antagonists, that is, drugs that block the actions of dopamine. Many of these treatments are sufficiently successful to enable patients to live and often work in society rather than face a lifetime of hospitalization, but they may not be the optimal treatments, are certainly not cures, and have proven ineffective in a large number of patients. Dopamine antagonists also produce unwanted side effects in the form of serious Parkinsonian-like symptoms such as muscle rigidity.

In the past decade, we have come to recognize that many of these patients who did not benefit from treatment with dopamine antagonists can be treated effectively with another drug, clozapine, that is relatively weak as a dopamine antagonist but is also an antagonist at receptors for several other neurotransmitters, including serotonin. Serotonin is the neurotransmitter that is believed to mediate the psychological effects of both hallucinogens and entactogens. Clozapine has also proven to be remarkable in that it achieves its therapeutic effects in schizophrenia patients without producing Parkinsonian-like side-effects. It does, however, produce potentially fatal blood abnormalities in perhaps 1% of patients and is, therefore, both risky and costly. Given the devastating lifetime nature of schizophrenia, these risks and costs are often deemed acceptable by patients, families, and physicians, largely because the clozapine treatment can be so remarkably effective. Thus, the key message is that these treatment-resistant patients, who have failed to respond to any number of dopamine antagonists, can be treated pharmacologically and can again lead relatively productive lives. Accordingly, the search has been intense to understand the therapeutic mechanism(s) of action of clozapine and to identify new drugs that would have similar therapeutic effects without the potentially fatal side-effects. One of the candidates for such a drug is what could aptly be called a hallucinogen antagonist that has been identified directly by animal studies of hallucinogen mechanisms.

Schizophrenia

Theories regarding the abnormalities responsible for the symptomatology of the group of disorders we call schizophrenia have often suggested the importance of deficits in early forms of filtering, gating, and information processing. Such theories posit that deficient gating of sensory and cognitive information results in an overloading inundation of information and consequent disorganization of thought processes (the hallmark of schizophrenia) (e.g. Braff and Geyer, 1990). In parallel, the actions of hallucinogens have often been related to changes in filtering mechanisms, e.g. the doors of perception described by Aldous Huxley. Many investigators have suggested that an understanding of the mechanisms contributing to effects of these drugs could provide insight into the abnormalities of brain function that lead to psychotic disorders. It is not necessary to argue that hallucinogens mimic all the symptoms of a complex disorder such as schizophrenia to believe that they affect some of the same brain systems that can be disturbed in psychiatric illnesses (Geyer and Markou, 1995). Thus, an understanding of hallucinogen actions may be relevant to specific aspects of schizophrenia rather than the entire complex syndrome. In recent years, this idea of gating or filtering deficits in schizophrenia has been studied successfully using measures of startle responses. A number of experiments have used laboratory animals to explore the similarities between the effects of so-called psychotomimetic drugs and the abnormalities of information processing observed in patients with schizophrenia or related disorders. Our group has taken advantage of the opportunity for cross-species studies of information processing provided by startle response tests. Specifically, two examples of fundamental filtering mechanisms we have studied using the startle response are habituation and prepulse inhibition (PPI).

Startle Measures of Information Processing

The startle reflex is a collection of responses to sudden intense stimuli that has provided a useful approach to studying the neural control of simple behaviors. One major advantage of startle response paradigms is that similar behavioral phenomena can be studied in a variety of species (Geyer and Markou, 1995). In humans, the blink reflex component of the startle response is measured using EMG. In small animals, a movement sensor is used to measure the whole-body flinch elicited by startling stimuli. Of importance for the present work is not the reflex phenomenon itself, but two conceptually important forms of information processing - habituation and PPI - that can be demonstrated using measures of startle. One is habituation, which is often considered to be the simplest form of learning. Habituation is defined as the decrease in responding when the same stimulus is presented repeatedly. For example, habituation enables us to learn to ignore the repetitive but unimportant ticking of a clock. The process of habituation is essential to the selectivity of attention, since only by learning to ignore irrelevant stimuli (i.e. habituate) can one focus attention specifically on significant events. Another form of information processing is PPI, which is the normal suppression of the startle reflex when the intense startling stimulus is preceded by a weak prestimulus. In PPI, a weak prepulse inhibits the behavioral response to a powerful sensory stimulus. In all animals tested, PPI occurs when the prepulse and startling stimuli are in the same or different sensory modalities. It does not appear to be a form of learning, since it occurs on the first exposure to the prepulse and pulse stimuli, and it does not exhibit habituation over multiple tests. PPI is considered to be an example of a pre-attentive and largely involuntary filtering mechanism because of the very short time interval between the prepulse and the startle stimulus (i.e. 30-300 msec) that is sufficient to produce the inhibition. In contrast, habituation operates at much longer time frames and involves the cognitive processing of the information content of the stimuli.

Startle Habituation in Schizophrenia

In keeping with the theory that schizophrenia is characterized by an inability to inhibit responding to unimportant events, the habituation of acoustic startle (startle elicited by bursts of noise presented through headphones) is deficient in patients with schizophrenia (Geyer and Braff, 1982; Braff et al., 1992). Relative to either normal controls or non-psychotic psychiatric patients, actively ill patients with schizophrenia were found to exhibit a slower rate of habituation, that is, they continued to respond to the noises longer than the controls even though the noises had no particular meaning. It is important to note that all three groups were similar in response to the initial presentations of the startling noises. Thus, the deficit in habituation was seen in the absence of any change in startle reactivity, consistent with the notion that the abnormality involves the processing of information rather than basic sensory reactivity. Others have reported similar deficits in the habituation of cutaneous startle (elicited by tiny electric shocks) in psychotic patients, also in the absence of differences in startle reactivity (Bolino et al., 1994). The observation of deficits in both acoustic and cutaneous startle habituation indicates some generality in the phenomenon. Deficits in habituation in schizophrenia patients do not simply result from medications or psychotic behavior per se, since schizotypal patients who exhibit behavioral abnormalities but are not receiving antipsychotic medications and are not grossly psychotic also show

habituation deficits (Cadenhead et al., 1993). If such deficits in habituation can be generalized to other sensory input and response output systems, perhaps even including thoughts to which most of us readily habituate, patients having such an abnormality would be expected to have difficulties in organizing a coherent view of the world - they would literally be unable to differentiate important from unimportant events or direct their attention selectively to specific stimuli or thoughts.

Startle Habituation in Animals

Studies in rats have suggested that brain serotonergic systems, which are defined by the neurons that use serotonin as their neurotransmitter, control startle habituation. These effects appear to be due to the activation specifically of one of the several subtypes of the brain's receptors for serotonin, the serotonin-2 receptor. The effects of hallucinogens are believed to be due largely to their actions as serotonin-2 agonists, that is, they mimic the effects of serotonin at these particular receptors. Hallucinogens have often been suggested to enhance one's ability to see familiar things as novel and to increase the perceptual impact of both external events and internal thoughts. While such an experience may be desirable in one who knows that the distortion of information processing is due to the ingestion of a drug and is time-limited, it must be quite a different experience to recognize that this condition reflects the permanent status of one's brain. In animals, of course, we study effects of these drugs in the absence of insight about the source of the perceived abnormality - rather like studies of LSD in which the drug was given to subjects without their knowledge. Relatively early studies demonstrated that the hallucinogens LSD and mescaline impaired the habituation of tactile startle (elicited by small puffs of air) in rats (Geyer et al., 1978; Geyer and Tapson 1988). Similarly, Davis et al. (1986) demonstrated robust increases in acoustic startle in rats treated with mescaline that were not associated with any change in the initial level of startle reactivity and appeared to be attributable to a specific effect on the habituation of startle. In contrast, amphetamine increased startle on all trials, reflecting a more generalized increase in startle reactivity (Davis et al., 1986). This study was among the first to implicate serotonin-2 receptors in startle habituation, as the effect of mescaline, but not that of amphetamine, was abolished by pretreatment with the serotonin-2 antagonist ritanserin. Subsequent studies with a variety of serotonin-2 antagonists demonstrated that the antagonists by themselves could accelerate tactile startle habituation (Geyer and Tapson, 1988). Thus, the opposite effects of hallucinogenic serotonin-2 agonists and serotonin-2 antagonists in the modulation of startle habituation provide strong support for the use of these hallucinogens as models of the parallel deficits in gating functions observed in schizophrenic and schizotypal patients. Furthermore, they support the idea that the special therapeutic actions of the antipsychotic clozapine may be related to its serotonin-2 antagonist properties and that selective serotonin-2 antagonists (i.e. hallucinogen antagonists) might help at least some patients with schizophrenia.

The effects of "entactogens" on habituation in rats further implicate the serotonergic system in the control of startle habituation. These drugs, including 3,4-methylenedioxy-N-methyl amphetamine (MDMA or "Ecstasy") and alpha-ethyltryptamine (AET or "Love Pearls"), are potent releasers of serotonin from neurons in the brain and robustly impair the habituation of startle responses (Kehne et al., 1992; Martinez and Geyer, 1997). The anti-habituation effects of serotonin releasers are prevented by pretreatment with serotonin reuptake inhibitors, such as fluoxetine ("Prozac"), which prevent the drug-induced release of serotonin from serotonergic (but not dopaminergic) neurons (Kehne et al., 1992; Martinez and Geyer, 1997). Thus, it appears that these entactogens impair habituation by releasing serotonin, which then presumably acts upon serotonin-2 receptors.

The psychotomimetic agent phencyclidine (PCP) also impairs the habituation of startle responding in rats, especially at relatively low doses (Geyer et al., 1984). Thus, impairments of startle habituation appear to constitute a behavioral effect in rats that is common to hallucinogenic serotonin agonists, entactogenic serotonin releasers, or psychotomimetic PCP-like drugs.

Prepulse Inhibition in Schizophrenia

Prepulse inhibition of acoustic startle is deficient in schizophrenia patients (Braff et al., 1978). Theoretically, such a deficit in a fundamental form of pre-attentive filtering may distort information and produce a form of sensory overload which may lead to the disorganized thought processes that are the hallmark symptoms of schizophrenia. This deficit in PPI has been confirmed in studies of medicated, but still-ill patients with schizophrenia in various countries and by investigators using different methods (Bolino et al., 1994; Braff et al., 1992; Grillon et al., 1992). As with habituation, non-medicated schizotypal patients also show PPI deficits (Cadenhead et al., 1993). Furthermore, there is some evidence that PPI deficits in schizophrenia may be reversed by successful treatment with antipsychotic drugs (Hamm et al., 1995; Weike et al., 1996). Only recently have studies attempted to relate these observed deficits in sensorimotor gating functions to measures of thought disorder. Perry and Braff (1994) have reported a significant correlation within a group

of schizophrenia patients between deficits in PPI and thought disorder as assessed by psychological tests. Further studies in this vein will be important in relating the abnormalities in basic forms of information processing, such as PPI or habituation, to more complex symptoms, treatment outcomes, or quality of life.

Prepulse Inhibition in Animals

In rats, hallucinogenic serotonin agonists have been found to disrupt PPI, mimicking the deficit in PPI observed in schizophrenia patients. LSD, which mimics the effects of serotonin (i.e. has agonist effects) at multiple serotonin receptors, dose-dependently reduces PPI (Geyer, in press). Similarly, PPI is reduced by hallucinogens that have more selective agonist effects at serotonin-2 receptors, such as 2,5-dimethoxy-4-iodoamphetamine (DOI). Importantly, the PPI-disruptive effects of hallucinogenic serotonin-2 receptor agonists are blocked by pretreatment with serotonin-2 antagonists including MDL 100907 (Padich et al., 1996; Sipes and Geyer, 1994, 1995), but not by the dopamine antagonist and traditional antipsychotic haloperidol (Padich et al., 1996). Such findings have contributed to the current investigation of MDL 100907 as a possible non-dopaminergic antipsychotic in patients with schizophrenia. Because MDL 100907 is devoid of dopamine antagonist properties, it will not produce the Parkinsonian-like side-effects that plague the current class of antipsychotics. This drug is currently (1997) being tested in clinical trials; early reports from these trials have been promising. If it does prove to be antipsychotic, it will represent one of the very few novel treatments used to treat schizophrenia that is not based on any dopamine antagonist effects. Thus, it may be particularly effective in the subgroup of schizophrenia patients for whom dopamine antagonists are ineffective. Clearly, if this promise is realized, it will be a direct benefit of animal studies on the mechanisms responsible for the effects of hallucinogens.

PPI in rats is also reduced by systemic treatment with serotonin releasers, or "entactogens", including MDMA, N-ethyl-3,4-methylenedioxy-amphetamine (MDEA or "Eve"), fenfluramine, and AET (Kehne et al., 1992, 1996; Mansbach et al., 1989; Martinez and Geyer, 1997). The PPI-disruptive effects of serotonin releasers are prevented by pretreatment with the serotonin reuptake inhibitor fluoxetine, which prevents the drug-induced release of serotonin from serotonin neurons while having little effect by itself. As with the classical hallucinogens, the serotonin-2 antagonist MDL 100907 and possible new antipsychotic is also effective in blocking the effects of serotonin releasers on PPI (Padich et al., 1996). Thus, it appears that these entactogens disrupt PPI by releasing serotonin which, in turn, acts upon serotonin-2 receptors.

In rats, PPI is reduced dose-dependently by the administration of the psychotomimetic PCP or related drugs such as ketamine (Mansbach and Geyer 1989, 1991). Importantly, the effects of PCP are <u>not</u> reversed by typical antipsychotics such as haloperidol, but <u>are</u> reversed by atypical antipsychotics including clozapine (Bakshi et al., 1994; Geyer et al., 1990). Thus, the PCP-disruption of PPI may be a useful model for identifying novel atypical antipsychotic treatments. In humans, this class of drugs produces symptoms that mimic some features of schizophrenia (Javitt and Zukin, 1991). Specifically, PCP-induced clinical effects have been linked to the characteristics and pathophysiology of the "deficit" symptoms of schizophrenia that are the most difficult to treat with the typical antipsychotics that work via dopamine antagonism. Furthermore, ketamine has been shown to produce a schizophrenia-like deficit in PPI in normal control subjects (Karper et al., 1994), induce psychotic symptoms in normal volunteers (Malhotra et al., 1996), and exacerbate psychotic symptoms in schizophrenia patients (Lahti et al., 1995), providing some validation of the similar animal studies.

Conclusions

The study of gating or filtering deficits in schizophrenia and parallel animal models based on startle measures of information processing has demonstrated considerable utility in the exploration of the phenomenology and neurobiology of schizophrenia in general and the drug-induced models of psychosis in particular. In rats, hallucinogens, entactogens, and PCP-like drugs mimic both the impairments of habituation and disruptions in PPI observed in patients with schizophrenia. Either of these abnormalities could be responsible for the thought disorder that is central to the symptoms of schizophrenia. The effects of hallucinogens and entactogens on both habituation and PPI have been related to their particular mechanisms of action within serotonergic systems. These observations in rats have led directly to the development of serotonin-2 antagonists for the treatment of schizophrenia. The effects of PCP and related psychotomimetics in rats appear to be sensitive specifically to atypical antipsychotics and may aid in the identification of novel antipsychotic therapeutics. By virtue of the extensive knowledge regarding the neurobiological substrates involved in the modulation of such gating functions as habituation and PPI in laboratory animals, the further application of these measures may enable the elucidation of both the mechanisms of action of psychotomimetics in humans and their possible relevance to the abnormalities that lead to schizophrenia and related psychotic disorders.

Shortly after the discovery of the neurotransmitter serotonin, it was suggested that LSD might owe its profound effects to actions on serotonin systems in the brain, due to structural similarities between LSD and serotonin. It was also suggested that we might learn something about the causes and/or treatment of psychotic disorders by discovering the mechanisms of action of LSD and related hallucinogens. While European psychiatrists have continued to explore this possibility (Hermle et al., 1993), most American psychiatrists dismissed the idea some 30 years ago because of largely specious arguments (Geyer and Markou, 1995). In retrospect, one can argue that the current excitement regarding the potential effectiveness of a serotonin-2 antagonist such as MDL 100907 in the treatment of schizophrenia could and would have been explored long ago if animal studies of hallucinogens had been supported more widely. Instead, progress has been slow, being based on the work of relatively few laboratories. For many years, it was thought that LSD functioned as a serotonin antagonist and that serotonin acted as a tranquilizing neurotransmitter in opposition to the activations associated with the neurotransmitter dopamine. Subsequent studies in animals revealed that LSD and related compounds actually act as serotonin agonists, that is, they mimic some actions of serotonin (at the serotonin-2 subtype of serotonin receptors). Although entrenched ideas fade slowly, informed neuroscientists are now recognizing that serotonin and dopamine are not simply reciprocal neurotransmitter systems and often work in concert. Hence, it is now acknowledged that both serotonin antagonism and dopamine antagonism may contribute importantly to the treatment of psychosis. This new insight, with its practical consequence being the current testing of a hallucinogen antagonist in schizophrenia patients, has evolved directly from multidisciplinary studies of laboratory animals. These animal studies may not have been motivated explicitly by the possible discovery of new treatments for any disease; most were designed simply to further our basic knowledge of serotonin systems and the mechanisms of action of hallucinogenic drugs. Without such basic knowledge, however, one can be confident that biomedical science will not advance and new treatments for psychiatric disorders will not be developed. Thus, despite the fact that such research is subject to ridicule by those who would stop animal research, I contend that animal studies of hallucinogen mechanisms have the potential to alleviate human sufferring.

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