Neuropsychopharmacology concepts: overview and analysis

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Introduction

This research paper was written explore and demonstrate my personal interests in my field of study, neuropsychopharmacology. The research papers discussed were selected to provide a diverse range of topics within the field, and to convey findings that I've deemed to be particularly unique or useful in real-life application.

Neuropsychopharmacology: a Brief, Multidimensional View

Although frequently demonstrated to be neurotoxic in humans, amphetamines have been therapeutically prescribed and abused recreationally since their discovery over a century ago. One form of amphetamine, infamous for its high rates of addiction and toxicity in users, is methamphetamine (METH). The researchers of this study posed the question of whether the traditional animal models demonstrating that METH use decreases caudate-putamen dopamine levels (DA) can be applied to human patterns of abuse and resulting neurotoxicity. Substantial research has indicated that tolerance to METH reduces many of the toxic effects associated with binge use of the drug. To demonstrate this, the researchers aimed to find if the neural death in rats associated with an acute METH binge following an escalation-dose (ED) pretreatment would be less severe than the damages stereotypically observed after high dose " binge" exposure without prior ED treatment. The researchers hypothesized that current research overstates the neurotoxicity associated with METH abuse, since

animal model studies fail to account for the ED pattern typically observed before binge-use in most human users of METH.

To test their hypothesis, the researchers selected groups of healthy male rats for experimentation. The living conditions of the rats were kept stable and relatively natural. Following a normalization period of at least a week, the rats were administered three separate, increasing doses of d-METH each day for two weeks. The period began with a dosage of 0. 1mg/kg and finished with a dosage of 4. 0mg/kg, a dose considered extraordinarily high for human users. Following the last day of ED pretreatment, the rats were administered a “ binge” regimen, consistent with those traditionally used in similar studies, of four injections of 6mg/kg at two hour intervals. Throughout the experiment, a variety of data regarding behavioral responses to the drug, physiological responses like hyperthermia, and other immediately observable variables were gathered. Three days after the last METH administration, the rats were killed and their brains were analyzed to measure DA content and the levels of DAT transporter binding that is typically reduced as a result of METH binge use.

Analysis of the data showed that the acute METH binge administration produced lower than average neurotoxicity in rats that were subject to ED pretreatment. All but one of the post-mortem neural tissue measurements displayed a reduction in damages in the pretreated rats while non-pretreated rats displayed normal levels of neural death following the acute binge. *In vitro* data showed similar results; rats administered the binge regiment without pretreatment displayed stereotypic movement associated with acute an METH binge. Most significantly, the data showed that the reduction in DA

levels typically resulting from METH binge administration was considerably less severe in the rats that underwent ED pretreatment. All p values for this data were less than 0. 01 or 0. 001.

The researchers concluded that a significant portion of the neurotoxic effects of METH binge use observed in rats can be attenuated by a prior escalation dose regimen. Since past studies on METH's neurotoxicity fail to examine the drug's neurotoxicity in subjects that followed " regular" human patterns prior to administration of toxic doses, the researchers argued that future research on stimulant abuse should follow an escalation dose pretreatment in order to produce data that is actually applicable to the majority of human subjects. For psychopharmacology researchers concerned with reducing drug related harm, this is extremely important information and future studies should explore further by finding a rodent ED pretreatment that is most comparable to actual human behavior patterns.

The effects of hallucinogenic drugs like psilocybin and LSD have been documented to profoundly alter visual perceptions of the world. For thousands of years, psilocybin and similar substance have been used for spiritual and religious rituals in many different cultures. Until recently, the neurological causes for the visual distortions have been largely unknown. Past research has found that the serotonin receptors, 5-HT2A, 5-HT2B, 5-HT2C, are likely highly involved in visual processing as well as hallucinations associated with Schizophrenia and Parkinson's disease. Past animal studies indicate that activation of the 5-HT2A receptors increases the excitability of the visual cortex. This research paper, published by the *Journal of Neuroscience* , investigates the possibility that the activation of 5-HT2A

receptors through psilocybin causes modulation of parietal-occipital α oscillations, resulting this noted increase in excitability of visual processors. The researchers further hypothesized that the hallucinations could be caused by the 5-HT2A receptor modulation of the visual cortex's visual recognition " potentials." Specifically, the researchers questioned whether or not the P1 and N170 (visual recognition and mid-level processing potentials) are modulated by psilocybin's activations of the 5-HT2A receptors.

The researchers attempted to answer these questions by administering across multiple doses a combination of psilocybin, a placebo, and ketanserin (a 5-HT2A antagonist to cancel the effects of psilocybin in certain trials) to seventeen healthy individuals on four different experimental days. After administration of each drug(s), visual stimulus and response tests were carried out with continuous EEG monitoring during each trial. α waves were measured for a short duration before and after the administration of the visual stimulus, and the resulting strengths were compared. Six hours after the administration of the drugs, the subjects were required to fill out a standardized questionnaire addressing their subjective visual alterations and changes in perception as a result of the drugs administered on that day. A variety of corrections and comparisons were performed on the data to analyze it with respect to the hypotheses, and results were constructed from the implicated correlations.

The first finding was that all subjects administered psilocybin subjectively experienced hallucinogenic effects or visual distortions. It was also found that the all subjects administered the placebo or ketanserin reported no hallucinations or visual distortions. P and r values for these data suggested

very strong replicability and correlation. From the α oscillation data, the researchers found that, under normal conditions, the α oscillations were stronger during the prestimulus phase than the poststimulus phase. From the psilocybin administered subject trials, the researchers found that the α oscillations were weaker than usual in the prestimulus phase and the subsequent reduction of strength was not observed in the poststimulus phase. In the placebo and ketanserin tests, no attenuation of α oscillations were observed. Similarly, in trials where ketanserin was administered 1 hour following psilocybin administration, the decrease in α oscillations was not observed, indicating that the 5-HT activation following psilocybin administration is likely a cause for the observed α oscillation modulation. Since α oscillations have been shown to be involved in the brain's construction of vision, the researchers concluded that the hallucinogenic effects of psilocybin are, at least partially, caused by modulation of α oscillations by activation of 5-HT2A.

Along with the modulation of α oscillations through psilocybin's activation of 5-HT2A, the researchers also monitored modulation of the P1 and N170 potentials. Activation of 5-HT2A was found to decrease the P1 potentials while increasing the N170 potentials during stimulus. Differences between the psilocybin and non-psilocybin trials showed trends and replicability similar to the observed α oscillation data. Since these potentials have been shown to be important neurological processes associated with the brain's recognition and construction of visual input, the researchers concluded that modulation of these important visual potentials is likely somewhat responsible for the perceived changes in visual perception. These data are

among the first to show a potential neurological mechanism of action for the changes in visual perception caused by psilocybin, and future research could seek to understand how the modulation of these systems directly relates to specific visual changes.

Alcoholism is an affliction facing millions of people worldwide and its consequences stretch far beyond the individual. Despite the mounting medical and social costs of alcohol addiction, little progress has been made towards developing effective medication as treatment. Ibogaine, a hallucinogen found in a plant native to Africa, has been anecdotally observed to reverse or undue addiction to many drugs of abuse, including alcohol. Due to its safety profile and nature of the drug's effects, ibogaine has not yet been considered a potential medication. In this study, the researchers posed the question of whether ibogaine reduces behaviors of addiction; and, if so, how and where it produces these effects in the brain. Digging deeper, the researchers aimed to refute or confirm evidence indicating that ibogaine causes neurotoxicity at doses associated with the addiction reducing action of the drug.

To answer these questions, the researchers used both behavior studies and in vivo `brain analysis. The behavior studies, testing the anti-addiction potential of ibogaine, were carried out by habituating rats to ethanol (self-administered or systematically) and then recording preferences following treatment with ibogaine. One study allowed the rats continuous access to both water and ethanol for a period of two months before administration of alcohol. In another study, rats were placed in a cage with two levers, one delivering water and the other delivering ethanol. After a period of three

days without the water lever being active, ibogaine was administered and the responses were recorded. A variety of similar experiments were carried out, each of them aiming to eliminate one area of uncertainty regarding the nonspecific activities of the drug.

To test for the mechanisms involved in ibogaines addiction reversal, the researchers carried out a series of ibogaine microinjections into the brains of ethanol self-administering rats. In order to clarify which area of the brain is mediates ibogaines effects, each injection was localized at a different brain structure associated with addiction and the resulting behaviors were observed. In vivo, the researchers further isolated ibogaines mechanism of action by examining the drug's effects on cells in the rodent's midbrain. To test for neurotoxicity, the brains of non-ibogaine treated mice were analyzed against the brains of ibogaine treated mice.

After analyzing the data, the researchers found that all trials indicated attenuation of alcoholism in rats treated with ibogaine. With continuous access to alcohol before and after treatment, ibogaine treated subjects showed a reduction in preference for alcohol (when given a choice) as well as a reduction of intake when no choice was offered. Further clarifying the findings, the data showed that rats treated with ibogaine showed very little change in preference for water or sucrose control solutions. P values for these data was less than 0. 02 consistently. The findings confirm that ibogaine, when administered to alcohol preferring animals, reduces the animals consumption of alcohol.

Among the secondary findings, the researchers also determined the specific area mediating ibogaine's action to be the ventral tegmental area (VTA). In trials where ibogaine micoinjections were performed in the VTA, rats decreased their consumption of alcohol considerably. In trials where the same microinjections were made in neighboring substantia nigra, no reduction in alcohol was observed.

Another important result was the lack of cell death observed in mice treated with the same therapeutic doses administered to the rat subjects. This was found by observing comparing brain sections of mice exposed to known neurotoxins, ibogaine, or nothing. Similarly, no coordination impairment or bodily harm was found to occur after ibogaine administration at therapeutic doses.

The researchers also found that the expression of the glial cell line-derived neurotrophic factor (GDNF) is directly affected by the drug ibogaine. This leads to what is probably the most important discovery of the data: when GDNF neutralizing antibodies are injected into the VTA of ibogaine administered alcoholic rats, the reduction of alcohol intake was negated. These findings confirm previous studies that show GDNF negate some of the effects of psychoactive drugs.

The results of the experiment indicate that ibogaine is not only a potential treatment for alcoholism and addiction, but that this effect is likely carried out through increase in GDNF expression after administration of ibogaine. In the research field seeking to find treatment for drug abuse, these results are potentially revolutionary. To develop an effective treatment, future studies

could seek to develop a molecule that induces the upregulation of the GDNF pathway. Alternatively, further research could be done on ibogaine in order to develop a treatment that excludes the hallucinogenic effects of the drug.