DMT and Psilocybin Research

by Dr. Rick Strassman University of New Mexico Medical School

THE National Institute on Drug Abuse (NIDA) has scored highly a grant proposal to continue the clinical research with hallucinogens we have been performing since November, 1990. In all likelihood, funding will begin either late this year or early next. The grant proposal is for three additional years of projects, and the total award is for approximately $500,000. The National Institute on Drug Abuse grant will support three DMT studies, and one psilocybin study.

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DMT Pretreatment Studies

Two of the DMT studies involve attempts to modify DMT's biological and psychological effects by pre-treating subjects with drugs believed to have an effect on brain areas affected by DMT. DMT's effects, like those of other "classical hallucinogens" such as LSD, psilocybin, and mescaline, are probably caused by an interaction with certain nerve cells contained within the brain. These cells are part of the serotonin system. Serotonin is a chemical, a neurotransmitter, which allows nerve cells to communicate with each other across tiny spaces, called "synapses." A serotonin-containing nerve cell which is stimulated beyond a certain threshold "fires," releasing serotonin into the synapse, which then attaches to specialized sites on the "receiving" nerve cell called "receptors." Serotonin attaches to its receptors, thus modifying the electrical activity of the receiving cell, which in turn either fires itself, or is prevented from firing. There are several varieties of serotonin receptors, called "subtypes," including the type "1A," "1B," "1C," "1D," "1E," "2," "3," and "4." Psychedelics are most strongly bound to the 1A, 1C, and 2 subtypes.

Drugs which block serotonin-2, -1C, and -1A subtypes have been found to block the effects of hallucinogens in lower animals. However, tests of "hallucino-genicity" in lower animals are open to criticism because of the difficulty in knowing exactly what the animal is responding to. Clearly, human studies are necessary to refute, confirm, or modify existing hypotheses generated by lower animals experiments. Thus, we are interested in determining which serotonin receptors, in man, mediate specific effects of DMT.

Our original DMT study demonstrated that DMT raised blood levels of beta-endorphin, cortisol, adrenal stimulating hormone, and prolactin; all of these hormones' regulation is believed controlled, to some extent, by serotonin receptors in the brain. In addition, we found rises in blood pressure, heart rate, pupil diameter, and core temperature in response to DMT; these variables also are regulated to some extent by serotonin nerve cells. Finally, we have carefully mapped out the psychological effects of DMT using the Hallucinogen Rating Scale, the development of which was discussed in a previous article. Now that we have this data describing effects of DMT by itself, we can pre-treat subjects with drugs that block certain types of serotonin receptors, and see what happens to these factors. For example, if pre-treatment with a serotonin-1A blocking drug enhances visual effects, but reduces beta-endorphin stimulation, we can suggest that the serotonin-1A receptor mediates those functions. These data could have use in developing antidotes for certain problematic reactions to psychedelics, and provide insights into important brain-mind interactions. They also might provide glimpses of understanding into spontaneous "psychedelic" states, such as some naturally occurring psychotic phenomena.

We have found a likely candidate for a serotonin-1A blocking drug, our first blockade project. However, we have been unsuccessful in locating a serotonin-2 and serotonin-1C drug, the second series of studies. These two latter receptors are extremely similar, and drugs that block the "2" subtype usually block the "1C" as well. There are several "2/1C" agents at various stages of development within human and animal studies, but so far, no one has agreed to provide such a drug to us. Efforts are continuing.

DMT Tolerance Study

The last DMT study is an attempt to develop tolerance to repeated administrations of DMT at one sitting. All other psychedelics, in man, have demonstrated tolerance to repeated administration. Thus, LSD at the same dose every day for three days, prevents that originally

active dose from having any effect on the fourth consecutive day. Several days drug-free are necessary to return to the previous level of sensitivity. DMT, administered twice a day (10 a.m. and 3 p.m.) for five days, in the only published human study that attempted to develop tolerance, demonstrated no tolerance. Animal studies have also given inconsistent results, with one study giving it every 2 hours for 21 days and finding only limited tolerance! Some animal studies have even suggested that sensitivity is increased depending on the timing and dose schedule. Finally, humans tolerant to LSD are not tolerant to DMT. Reports "from the field" are also not consistent. If any of you reading this have experience with repeated administration of DMT, I would be most interested in hearing about them.

THE importance of developing (or not developing) tolerance to DMT derives from at least two perspectives. One is the fact that the inability to generate tolerance to DMT in humans is one of DMT's strongest characteristics suggesting its role in spontaneous psychotic states. Recall that the discovery of DMT in human body fluids set off a flurry of investigations assessing whether it was involved in psychoses. If DMT does have a role in spontaneous hallucinations, and it were possible to develop tolerance to its effects with repeated and/or continuous exposure, then people would only hallucinate when tolerance was no longer in effect. However, that is contrary to clinical experience, inasmuch as people with psychotic illness often hallucinate continuously. Therefore, if we cannot develop tolerance, a role for DMT in mental illness would be supported. Secondly, the "tolerant state" is of great interest in the field of psychopharmacology. Why drugs "no longer work" when they used to is of practical importance in treatment of mental illness, understanding how psychoactive drugs (including alcohol, nicotine, cocaine, LSD, and others) work. Particularly with respect to hallucinogens, how a previously psychedelic dose of LSD could have no effect in someone with repeated exposure to the drug is a fascinating question for mind-brain researchers.

Our study will give the smallest dose of DMT four times, separated by one hour. We will gradually, in a small number of subjects, alternatingly shorten the interval to one-half hour if no increase or decrease in effect is seen with the low dose every hour. If no effect is noted with low dose every half-hour, we will try a higher dose every hour, then every half-hour, and so on, up to a possible high dose every half-hour. Enhanced effects of repeated dosing will be apparent with this systematic approach. Once we have found the right dose and interval, the full group of subjects will be in tolerance development, or lack thereof. In the unlikely event no tolerance is seen with repeated administrations, we might consider a slow continuous administration of IV DMT.

Psilocybin Study

Our last study of this three year project is an oral psilocybin dose-response study. This will be identical in nature to the original DMT study. A low and high dose of psilocybin will be given non-blind, to assess safety and comfort with the drug in the clinical research setting. Then, if subjects are still interested in participation, they will receive in a double-blind, randomized manner: placebo, high and low dose psilocybin again, and two intermediate psilocybin doses. Double-blind means that neither I nor the subject will know what particular dose is being administered that day. However, the pharmacist who prepares the drug will have this information if necessary. Randomized means that the order of dose or placebo is completely random. Blood for several hormones and psilocybin levels will be drawn throughout the day, and blood pressure, heart rate, body temperature, pupil diameter, and psychological effects assessed repeatedly. We are remodelling a room on the Clinical Research Center at the University of New Mexico Hospital, where all studies will take place, so as to provide a less "high-tech" atmosphere for the longer-acting psilocybin.

The majority of funds will go towards salary support for myself, a laboratory technician, and a psychiatric research nurse. In addition, first-year monies will go toward the syntheses of the psilocybin and remodelling of the research unit

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