SWISS RESEARCH UPDATE

swiss research with **psilocybin, ketamine, mdma** and other psychedelics

AT THIS TIME, OUR SWISS RESEARCH GROUP includes the author as coordinator and project leader/head, a post-doctoral candidate in neurobiology and seven doctoral candidates in medicine. Since January 1995 we have focused on the psychological and biochemical/physiological effects of psychedelics in healthy volunteers.

The positron emission tomography (PET) scan program of study encompasses three major avenues:

1. to investigate the locus of action of psychedelics in the human brain neuroreceptors through radioactive labeling,
2. to investigate neuroreceptor occupancy during hallucinatory states,
3. to search for putative alterations in these receptors/binding sites in schizophrenics.

In collaboration with the new PET department at the University Hospital Zürich (USZ, Dr. A. Buck) and the University of Bern (Prof. R. Brenneisen), we have already labeled 4-Iodo-2,5-dimethoxy-A (DOI) and psilocin. S-ketamine has also been labeled, in collaboration with the PET center at the Paul Scherrer Institute (PSI, Prof. K. Leenders) in Villigen. At this time, we have already done some initial monkey studies. The tracers must be proven to be suitable ligands before we can do human studies. The two psychedelics 4-Bromo-2,5-dimethoxy-A (DOB) and 4-(2-Fluoroethyl)-2,5-dimethoxy-A (DOEF) will be further candidates for labeling.

As previously shown, ketamine (racemic mixture) and psilocybin resulted in a hyperfrontal metabolic pattern in the human brain associated with hallucinations and ego-dissolution (Vollenweider et. al. 1994). Furthermore, we are investigating whether we can block these psychological and metabolic effects using different pharmacological blockers (serotonergic, dopaminergic and gabaergic drugs).

Pharmacological blockers

We have already shown that ketanserin (a 5-HT2 blocker) and risperidon (a 5-HT2 and D2 blocker) can completely block the psychological effects of psilocybin. We are also studying the effects of haloperidol (D2 blocker) on psilocybin-induced mental states. Concurrently, Dr. T. Baer, A. Baebler and S. Fretz of our department are studying the effects of such blockers (haloperidol, risperidon, ketanserin, midazolam) on ketamine-induced altered mental states. Classical rating scales (inventories) and computer-assisted neuropsychological tests are being used to investigate psychological alterations in cognition such as the "working memory," etc.

In collaboration with the PET center PSI-Villigen, we have started to investigate the effect of these blockers on the ketamine and psilocybin-induced metabolic changes using Fluoro-deoxyglucose-PET (FDG-PET). Also with the PET center PSI-Villigen, we have started to investigate dopamine receptor occupancy in psilocybin and ketamine subjects using PET scans. It is too early to discuss the results of either of these investigations.

Franz **Vollenweider,**
Psychiatric University Hospital Research Department
P. O. Box 68, CH-8029 Zürich, Switzerland
phone: 0041-1-384 21 11
Fax: 0041-1-383 51 14
e-mail: vollen@bli.unizh.ch

In collaboration with UC San Diego (UCSD), we will investigate the effect of these drug combinations on prepulse inhibition of the startle reflex. This method has been established with Mark Geyer, UCSD.

MDMA

In an upcoming series of investigations to be carried out with Alex Gamma, our neurobiologist, we will focus on the effect of MDMA on psychological and neurophysiological parameters in healthy controls using EEG/ERP, FDG-PET and prepulse inhibition. Putative alterations of these parameters will be compared with data obtained using the same methods in chronic MDMA users. These investigations will involve collaboration with the PET center, USZ and M. Geyer, UCSD.

S- and R-ketamine study completed

We have finished the S- and R-ketamine study using FDG-PET. The major findings are that S-ketamine resulted in a hyperfrontal pattern similar to that seen with the ketamine racemic mixture. Equimolar doses of R-ketamine resulted in a state of relaxation and in a hypofrontal metabolic pattern or in only slight changes. This study was completed in collaboration with the University of Oslo (Prof. I. Oye) and PSI-Villigen (Prof. K. Leenders).

We have finished a study on the oral (15-20 mg p.o.) and i.v. (1-5 mg) pharmacokinetics of psilocybin in healthy volunteers. The preliminary data show that psilocybin reactions after oral administration arise with psilocin plasma levels of 4-6 ng/ml, peak effects arise 80-90 minutes after oral administration and are associated with psilocin plasma levels ranging from 6-14 ng/ml (depending on the dose administrated). No psilocybin was found after oral administration, supporting the observations in animal studies that psilocybin gets immediately dephosphorylated and that psilocin may be the principle compound entering the brain. The analysis of the i.v. data are underway.

The study will go on investigating the pharmacokinetics of psilocin, since psilocin has been labeled for PET (in collaboration with the Pharmaceutical Institute University, Bern; Dres. F. Hasler and D. Bourquin). •

Vollenweider, F.X., Scharfetter, C., Leenders, K.L., and Angst, J. Disturbance of serotonergic or glutamatergic neurotransmission results in hyperfrontality as measured by PET and FDG in acute human model psychoses. European Neuropsychopharmacology, 367, 1994.

Hasler, F., Bourquin, D., Brenneisen, R.M., and Vollenweider, F.X. Pharmacokinetic profiles of oral and intravenous psilocybin. SOFT, 1995. Baltimore 1995 - 25th anniversary meeting October 9-14, 1995.