New Avenues in the Search for Biological Correlates of Altered States of Consciousness – From Model to Practice

by

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NOTE TO READERS: Dr. F.X. Vollenweider obtained his MD from the University of Zurich in 1986 and did a thesis in the field of experimental neurotoxicology at the Institute of Toxicology of the Swiss Federal Institute of Technology and the University of Zurich (1982-1986). From 1987-1989 he served as a Research Assistant in neurobiology at the Brain Research Institute, University of Zurich, particularly in the field of the neurochemistry and neurophysiology of the NMDA receptor. Dr. Vollenweider has been engaged at the PUK, Zurich (Burgholzli), since April 1989 and has been trained in Psychiatry and undergone 6 years of Freudian psychoanalysis. In addition to clinical work Dr. Vollenweider has also been actively concerned with basic research in the neurobiology of schizophrenia. In particular, since 1990 he has been responsible for the initiation and performance of the ongoing PET projects at the PUK. 1991 Dr. Vollenweider earned the "Twinning Grant 1991" (an achievement grant) given by the Swiss Society for Biological Psychiatry for his outstanding PET-project on model-psychosis.

In 1990 I initiated the PET project, "Brain energy metabolism in human experimental psychosis."

The Burgholzli-Tradition in Psychedelic-Research

For more than half a century, research work in the field of hallucinogens and related substances has been conducted at the Psychiatric University Hospital in Zurich. In 1926, Maier presented a monograph on cocainism [1]. In 1932, Wertham and Bleuler studied Rorschach-tests of volunteers who had taken mescaline [9]. In the late 1940's, Stoll [13], together with Condrau [8] did some clinical trials to study the effect of LSD-25 on schizophrenics.

More recently, as Professor J. Angst's directionship of the research department was established, the very real problems experienced by youngsters when they take hallucinogens and related drugs motivated us to continue the department's research in this field [2,11].

Dittrich initated and performed a series of studies to investigate with standardized methods (APZ) the psychic efffect of cannabinoids, dimethyltryptamine (DMT), psilocybin, nitrosoxide (N20), and nonpharmacological inducers of altered states of consciousness (sensory deprivation) in healthy volunteers. His work led to the publication in 1985 of a monograph on altered states of consciousness (ASC) demonstrating by dimensional analysis and algorithms of classical theory of mental testing that the main themes (content clusters) of ASC are three (oceanic feeling of merging with the cosmos, fearful ego-disintegration, perceptual changes of surroundings) and that they arise independent of the inducing technique [4,15]. Ego-disorders and perceptual changes are especially prominent features of psychedelic states as well as of "endogenous" psychotic states. Scharfetter developed an internationally accepted operationalization of the most important psychopathological terms [3]. He further developed and studied empirically a new differentiated approach to the psychopathology of schizophrenia [5]. He published about the differential diagnosis of hallucinations under various conditions [6] and presented a book entitled "Observations and Reflections on Delusions and Altered States of Consciousness" (1990, in print).

In 1990, I have been the motivating factor for the initiation of the PET project "Brain energy metabolism in human experimental psychosis" as described below [7,17].

"Chemical scalpels" for exploring the human mind

Hallucinogens and related drugs are remarkable "chemical scalpels" for exploring the human mind. They are useful laboratory tools in the study of the neurochemical changes associated with altered states of consciousness, variously experienced as psychotomimetic, psychedelic or mystical states.

Thus far, the analysis of psychedelic drug actions has been one of the most effective approaches to generate heuristic biochemical hypotheses underlying experimentally induced psychopathological conditions ("model-psychosis"). However, little attention has been paid to holistic neurophysiological explanations of psychedelic experiences.

This failure has both conceptual and methodological bases. The conceptual basis relates to the foundation of a biological theory of consciousness, insofar as the foundation of such a theory is restricted to inherent metaphysical issues, such as ontological and epistemiological constraints. However, the development of a physiological model of altered states of consciousnesss which is based on correlations between mental and neuronal activity is not beyond scientific methodology.

In this respect, the recent development of functional neuroimaging techniques such as the position emission tomography (PET) allows scientists to investigate neuronal activity throughout the brain by measuring brain energy metabolism in vivo in man . This approach brings together the disparate lines of neurochemistry, neurophysiology and psychology.

Research strategies to investigate biological correlates of altered states of consicousness using hallucinogens and PET (Positron-Emission-Tomography).

In 1990, the Psychiatric University Hospital (PUK), Research Department and the Paul Scherrer Institute (PSI), PET unit (Head: PD Dr. K.L. Leenders), have started a project to investigate the intra-individual effects of amphetamine, ketamine, and psilocybin on cerebral energy metabolism in a group of selected healthy volunteers. The practise and theory of "model-psychosis" as employed at the PUK is used as an experimental paradigm of schizophrenia. Brain energy metabolism is measured using PET and the radioligand [18-F]-fluorodeoxyglucose, a technology used on a routine basis at the PSI. The experimental protocols have been approved by the University Ethics Committee while the use of psychoative drugs has been approved by the Swiss Federal Health Office, Department for Pharmacology and Narcotics, in the Swiss capital city of Berne.

The psychoactive drugs used in this study are of paramound interest because they interfere with distinct neurotransmitter systems thought to be disturbed in schizophrenic psychosis. Amphetamine interferes predominantly with the catecholaminergic, psilocybin with the serotonergic and ketamine with the glutamanergic neurotransmitter systems. Moreover, during recent years schizophrenia research using PET technique has emphasized absolute or relative decreased metabolic activity in the frontal cortex (hypofrontality), while other PET-studies could not confirm this so-called hypofrontality but instead demonstrated bilateral hyperfrontality, hypertemporality and lateral asymmetries of glucose utilization. Hyperfrontality in acute and subacute schizophrenics seems to be associated with positive symptoms. However, whether these metabolic changes are a consequence or a cause of schizophrenic symptoms is not clear.

Therefore it is crucial and fundamental to know to what extend mental activity under psychotomimetic or psychedelic conditions contributes to cerebral metabolic changes.

Thus the first aim of the study was to investigate which brain regions metabolically respond to specific pharmacological stimulation under psychedelic conditions. A second aim will be to elucidate complex interrelationships between cerebral metablic changes and psychopathological alterations. Moreover, it is important to compare the metabolic data ("patterns") obtained from these "model psychoses" with the results of metabolic PET studies of schizophrenic patients. And last but not least, we think that such investigations will be decisive in the foundation of biological models of altered states of consciousness.

Outlook

A cortical-subcortical model of sensory information processing, the "complex-loop" model (CSTC-loops), is advanced to interpret psychedelic drug actions (for details see [7,16]). According to this model, psychotic and psychedelic symptoms may be produced by blocking neuronal information flow within cortical-striato-thalamo-cortical feedback-loops (CSTC-loops) resulting in a cortical overload of information, especially of the frontal cortex.

Indeed, our PET-data analysed so far indicate that ketamine and psilocybin induce different metabolic "patterns," but that both drugs dramatically stimulate

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glucose utlization in the frontal cortical regions (for details see [10,12,14]). This "hyperfrontality" corroborates the PET-findings as seen in acute hallucinating persons hospitalized for the first time with the diagnosis of schizophrenia, but stands in contrast to the observed "hypo-frontality" of chronic schizophrenics. Whether or not this "hyperfrontality" is a common feature of psychedelic mental states and acute hallucinatory phenom-enons as seen in schizophrenics remains open for further investigations.

The difference between ketamine and psilocybin is rather complex. Psilocybin significantly stimulates glucose uptake in the frontal and occipital brain regions only in the right brain hemisphere while ketamine does so in both hemispheres. Similarly, the insula, a part of the brain that is involved in language and hearing, is stimulated in both brain sides only under ketamine. A common characteristic of both drugs may be the disruption of the frontal-to-ventral striatal metabolic gradient, and a right brain side hyper-frontality.

Under subanesthetic conditions, ketamine blocks the NMDA receptor (glutaminergic neurotransmission) which seems to be involved in psychotic pro-cesses such as schizophrenia. And if there is a difference between ketamine and psilocybin induced effects, it is important because psychedelic experiences are not simply psychotic processes. ■

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