Hallucinogenic Drugs in Experimental Psychiatric Research

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Human experimentation with hallucinogenic drugs has an important tradition within psychiatric research. A main cornerstone of the early studies of the 1950 s and 1960 s was the model psychosis paradigm, which considers hallucinogen-induced states as suitable models for schizophrenic psychoses. Research was stimulated by the chemical similarity of hallucinogens and endogenous transmitters and the related hypotheses on the etiology of schizophrenic psychoses as autointoxications with false neurotransmitters due to metabolic abnormalities (transmethylation hypothesis, adrenochrome hypothesis). In the end, it was not possible to confirm these hypotheses. This was one reason why interest in this field of research faded at the end of the 1960 s. Moreover, at the same time research into psychedelics was discredited; mostly due to political reasons bound up the emerging problems of drug abuse and the worldwide scheduling of hallucinogenic drugs.

During the last 10 years there has been a revival of scientific interest in human experimental research with hallucinogenic drugs and, particularly, in the model psychosis paradigm. One important stimulus of this research was the discovery of the NMDA-antagonistic action of PCP and PCP-type hallucinogens, which provides a central argument for the glutamate hypothesis of schizophrenia. Recent studies have employed both the PCP-like anesthetic ketamine and classic psychedelic substances such as psilocybin and mescaline, and have used modern techniques auch as SPECT, PET and electrophysiological measurements.

The present issue of *Pharmacopsychiatry* provides a review of current human experimental research into hallucinogens and its related fields.

In their introductory paper, *Gouzoulis-Mayfrank* et al. report on the historical background of experimental research into psychedelic substances and summarize the rationale and potential of this research strategy for current psychiatric research.

Kovar gives an overview of the chemistry and pharmacology of hallucinogens, entactogens, and stimulants.

Geyer summarizes his studies on habituation and prepulse inhibition (PPI) of startle responses in laboratory animals under the influence of psychedelic drugs and in schizophrenic patients. Habituation and PPI are operational criteria of the sensorimotor gating or filtering deficits which have been suggested as contributing to cognitive disorganization in schizophrenics. Retardation of startle habituation and disruption of PPI were found in both animal models and in patients. These findings justify the use of hallucinogens in animal models as a first step to exploring the basic phenomena related to schizophrenic psychoses and as a way of developing and testing new antipsychotics.

Dittrich reports on his extensive experimental work in the 1970 s with various pharmacological (hallucinogenic drugs) and psychological (e.g. sensory deprivation, meditation) techniques for inducing altered states of consciousness (ASC). On the basis of this work *Dittrich* developed and validated the „APZ" questionnaire for the assessment of ASCs in healthy humans. This questionnaire avoids the methodological weaknesses of older tools, which either overemphasized negative effects or assessed effects predicated on psychoanalytic theories. The APZ questionnaire is currently used by the European groups performing human experimental work with hallucinogens.

Hermle et al. present the results of an open pilot study with mescaline and 12 healthy volunteers. Their data indicate the presence of a hyperfrontal cerebral metabolic pattern in the mescaline model psychosis. Similarly, *Vollenweider* reports on hyperfrontal cerebral metabolic patterns in the psilocybin and ketamine model psychoses. These findings differ from the majority of functional imaging studies with schizophrenic patients, which have repeatedly demonstrated hypofrontality. However, they correspond with a small number of studies with patients in acute phases of the illness presenting with prominent positive symptoms. Thus, data from the studies of *Hermle* et al. and *Vollenweider* correspond with the view that psychedelic states are suitable models for the acute stages of endogenous psychoses, but not for the nosological entity schizophrenia. *Abi-Saab* et al. reflect on the conceptual limitations of any drug model for schizophrenia, report on human studies with ketamine, and summarize the strengths of the NMDA antagonist model.

Schneider et al. discuss the possible associations between the endogenous anandamide/cannabinoid system and schizophrenic psychoses, and report on neuropsychological experiments with the 3-D inversion paradigm in healty volunteers

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intoxicated with Δ^9-THC. Their data demonstrate similarities in performance between productive schizophrenic patients and Δ^9-THC-intoxicated subjects, suggesting a similar disturbance in the internal, cognitive regulation of perceptual processes.

Finally, *Gouzoulis-Mayfrank* et al. reflect on methodological issues of human experimental studies with hallucinogens, including the selection criteria for experimental subjects, the problem of repeated measurements, and the need for adequate control substances. They present examples of recent experimental studies on facial expression and semantic priming, which take these aspects into account.

Human experimental research with hallucinogenic drugs is a potentially useful method for identifying linking variables between the psychopathologic conditions and neurobiological alterations involved in both pharmacologically induced and naturally occurring acute psychotic states. The contributions to this *Pharmacopsychiatry* issue substantiate the relevance of this traditional research strategy for modern biological psychiatric research. Using newly available powerful research tools such as functional imaging and electrophysiological techniques, the hallucinogen challenge paradigms are promising strategies which may enhance our understanding of the physiology and pathophysiology of mental operations and neuropsychiatric disorders.

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