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Disturbance of serotonergic or glutamatergic neurotransmission results in hyperfrontality as measured by PET and FDG in acute human model psychoses

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The cause(s) and pathophysiological significance of cerebral metabolic changes of glucose as seen in schizophrenics are not clear. Several PET studies emphasized – predominantly in chronic schizophrenics – decreased metabolic rates of glucose (CMRglu) in the frontal cortex ('hypofrontality'), while more recently two PET studies demonstrated increased frontocortical metabolism in acute schizophrenics with auditory hallucinations ('hyperfrontality').

To explore the relationship between cerebral energy metabolism and psychotic symptoms, we investigated the PCP/ketamine and the LSD/psilocybin models of schizophrenia, which suggest that in addition to a dopaminergic hyperactivity a deficient glutamatergic and/or excessive serotonergic activity may also be involved in schizophrenic disorders. The effects of ketamine and psilocybin on cerebral metabolism have been measured using PET and the radioligand [^{18}F]fluorodeoxyglucose in a group of healthy volunteers (n = 15). At subanesthetic dose ketamine preferentially blocks glutamatergic NMDA receptor mediated neurotransmission, while psilocybin increases serotonergic activity (Glennon, 1990; Vollenweider, 1992). Psycho(patho)logical ratings have been performed before and after each PET scan using the Altered States of Consciousness questionnaire (APZ), AMDP and EWL (mood) rating scales.

Ketamine (0.02–0.04 mg/kg/min, 60 min i.v.) induced somewhat more pronounced psychotic effects than psilocybin (10–20 mg p.o.) as indicated by the mean of APZ scores for 'oceanic boundlessness' (ket/psi: $9.3 \pm 2.5/7.3 \pm 2.5$), 'visionary restructuring' (ket/psi: $9.3 \pm 3.8/7.6 \pm 2.7$), and 'dread of ego dissolution' (ket/psi: $7.6 \pm 4.9/6.9 \pm 2.6$). Ketamine was more effective in inducing thought disorders, anxiety and apathy than psilocybin on AMDP subscales.

Both ketamine and psilocybin increased absolute (20–30%, $P < 0.01$) *and* relative (2–14%, $P < 0.02$) metabolic rates of glucose in frontal cortex. Ketamine increased the fronto-occipital (13–16%, $P < 0.02$) and inverted the midfrontal-ventrostriatal metabolic gradient in both hemispheres, psilocybin (11%, $P < 0.02$) only in the right. The change of the right midfrontal-ventrostriatal gradient was positively correlated with the schizophrenic syndrome. The change of the right hemispheric fronto-occipital gradient correlated with the schizophrenic syndrome (including hallucinations) under psilocybin, but only with the hallucinatory subsyndrome under ketamine.

The ketamine- and psilocybin-induced 'hyperfrontality' corroborates the PET findings in acute and untreated schizophrenics (Cleghorn et al., 1989), but stands in contrast to the observed 'hypofrontality' in chronic schizophrenics. The facts that ketamine and psilocybin induced an overlapping cluster of positive symptoms and that both drugs concomitantly inverted the midfrontal-ventrostriatal gradient support the idea that a cortico-subcortical neurotransmitter imbalance (glutamatergic/dopaminergic and/or serotonergic/dopaminergic) resulting in a increase of dopamine release may play a pivotal role in the generation of positive symptoms. Further investigation of the role of serotonin and glutamate in the pathogenesis of positive and negative symptoms is indicated.

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