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(+)-MK-801 induced social withdrawal in rats; a model for negative symptoms of schizophrenia

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Abstract

Dopaminergic agonists and NMDA-receptor antagonists form the basis for the dopamine and glutamate models of schizophrenia, respectively. In human subjects dopaminergic agonists evoke a psychosis resembling positive symptoms of schizophrenia, while NMDA-receptor antagonists produce both positive and negative symptoms. Consequently, the glutamate model may be considered the most complete of the two models. Alterations in animal behaviour, in response to amphetamine or NMDA-receptor antagonists, are widely used to model schizophrenia. NMDA-receptor antagonist induced social withdrawal in rat is an established model for negative symptoms of schizophrenia. In this study we have set up an automated method, based on video tracking, to assess social behaviour, motor activity and movement pattern in rats. This method was then used to evaluate the effects of amphetamine and the NMDA-receptor antagonist (+)-MK-801, administered as single intraperitoneal injections, on rat behaviour. Amphetamine caused significantly increased motor activity and a tendency towards stimulation of social interactions. (+)-MK-801 also stimulated motor activity, but induced a significant inhibition of social interactions. These results indicate that a single injection of (+)-MK-801 to rats models both positive and negative symptoms of schizophrenia. Amphetamine, in contrast, reflects only the positive symptoms of schizophrenia in this model.

Keywords: Amphetamine; (+)-MK-801; Negative symptoms; Rat; Schizophrenia; Social withdrawal; Video tracking

1. Introduction

1.1. Models for schizophrenia

The two main models or hypotheses for schizophrenia are the dopamine and the glutamate hypotheses for this disorder. The hyperdopaminergia model prevailed until the late 1980s when the glutamate model started to gain ground.

1.2. Amphetamine psychosis and the dopamine hypothesis for schizophrenia

Prolonged high dose self-administration, and occasionally even a single injection of amphetamine, are known to cause a psychosis typically characterized by paranoid delusions and hallucinations (Kokkinidis and Anisman, 1981; Young and Scoville, 1938), thus displaying resemblance to positive symptoms of schizophrenia (Beamish and Kiloh, 1960). This phenomenon has also been studied extensively under controlled conditions in the clinic with known doses (Angrist et al., 1974b). In individuals predisposed for developing schizophrenia even small doses of amphetamine may induce psychosis (West, 1974). On the other hand, low doses of amphetamine generally have beneficial effects on performance, attention, mood, social

Abbreviations: D2-receptor, dopaminergic D2-receptor; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine.

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abilities and results in intelligence tests (Weiner, 1964). There are no convincing reports of dopaminergic stimulators inducing behavioural or mental aberrations resembling negative symptoms of schizophrenia. Amphetamine has even been suggested to have a mitigating effect on negative symptoms in some schizophrenics (Sanfilipo et al., 1996; Van Kammen and Boronow, 1988).

Amphetamines augment dopaminergic and noradrenergic neurotransmission by inducing catecholamine release and preventing catecholamine reuptake. Although the effect is not specific for dopamine, the prevailing view is that dopaminergic mechanisms underlie amphetamine psychosis. Furthermore, virtually all currently used antipsychotic agents suppress dopaminergic neurotransmission. Reports of at least some of these drugs alleviating symptoms of amphetamine psychosis (Angrist et al., 1974a; Jha and Fourie, 1999; Misra and Kofoed, 1997) provide support for both the dopamine hypothesis and the amphetamine model for schizophrenia. The dopamine hypothesis is further supported by the fact that patients suffering from Parkinson's disease (PD) are known to develop paranoid delusions and hallucinations, mainly visual, following sustained (>1 year) L-DOPA treatment (Goetz et al., 1998; Klawans, 1988). It has been reported that PD patients with latent psychotic illness may experience hallucinations much sooner (<3 months) after onset of L-DOPA treatment (Goetz et al., 1998).

1.3. The phencyclidine or glutamate model for schizophrenia

The first and most striking support for the glutamate or phencyclidine model for schizophrenia is provided by the observation that phencyclidine (PCP) induces a psychotic state that includes both positive and negative symptoms in healthy individuals (Luby et al., 1959; Snyder, 1980). It should be recalled in this context, however, that the glutamate receptor blocking properties of PCP were not disclosed until 1982 (Lodge and Anis, 1982). Later, psychotomimetic effects were demonstrated with ketamine as well (Tamminga, 1999). Interestingly, Tamminga et al. (Lahti et al., 1995, 2001; Tamminga, 1999) found that schizophrenic patients exposed to ketamine experienced worsening or reappearance of positive symptoms characteristic of their individual psychoses. Surprisingly, these patients did not experience worsening of negative symptoms. This was hypothesized to be due to the high baseline in these individuals, with respect to negative symptoms, leading to a ceiling effect.

PCP, ketamine and the hitherto not mentioned substance (+)-MK-801 (MK-801) all belong to a group of non-competitive antagonists acting at the glutamatergic *N*-methyl-D-aspartate (NMDA)-receptor complex, binding to a site located within the ion channel and blocking cation flow. Due to the location of the binding site, the ion channel needs to be open for these antagonists to bind, thus making the antagonism agonist dependent. Among these NMDA-receptor antagonists, MK-801 is by far the most potent (Lodge et al., 1994).

1.4. Advantage of the glutamate model

Psychosis resulting from dopaminergic stimulation indeed shares many similarities with positive symptoms of schizophrenia, but does not include any characteristics that match negative symptoms. Furthermore, classic neuroleptics with pronounced dopamine D2-receptor blockade do not, in general, alleviate the negative symptoms in schizophrenic patients (see Blin, 1999). Taken together, these observations indicate that hyperdopaminergia is not directly responsible for negative symptoms in schizophrenia. In contrast, as mentioned above, dopamine agonists have been used successfully to treat negative symptoms.

NMDA-receptor antagonists on the other hand produce a psychotic state that includes both negative and positive symptoms. Furthermore, at least L-DOPA induced psychosis typically involves visual hallucinations, whereas NMDA-receptor antagonists reportedly cause auditory hallucinations (Allen and Young, 1978). The hallucinations in schizophrenia are considered to be mainly auditory, often consisting of inner voices. Thus, we may conclude that NMDA-receptor antagonists provide a more complete model for schizophrenia than do dopaminergic agonists.

1.5. Animal models for schizophrenia

NMDA-receptor antagonists and dopaminergic agonists administered to mammals constitute two widely used animal models for schizophrenia. Behavioural studies performed in rodents treated with these substances reveal behaviours that correspond to different symptoms of schizophrenia. The perhaps most studied behavioural aspect is motor activity. Drug induced hyperactivity in rodents may correspond to positive symptoms of schizophrenia (Nilsson et al., 2004; Sams-Dodd et al., 1997). Cognitive deficits may be modelled with memory and learning tasks (Arnt, 1998).

Social withdrawal is a core negative symptom in schizophrenia and may be modelled by various drug treatments in animals (Sams-Dodd et al., 1997). The prevailing view seems to be that unlike NMDA-receptor antagonists amphetamine does not induce social withdrawal (Sams-Dodd, 1995a, 1998b), although there are reports of amphetamine hampering social behaviour in non-human primates (Castner et al., 2004). However, this latter finding does not tally with observations in human subjects.

It should be mentioned in this context that social withdrawal in rodents is also used for modelling anxiety (File, 1980; File and Seth, 2003). However, in the literature NMDA-receptor antagonists are described as being both anxiolytic (Wieronska et al., 2003) and anxiogenic (File and Seth, 2003). Furthermore, the anxiolytic drug diazepam does not seem to reverse PCP induced social withdrawal in rats (Boulay et al., 2004; Sams-Dodd, 1998a).