THE EFFECT OF HALOPERIDOL AND CLOZAPINE ON THE BEHAVIOURAL CONSEQUENCES OF STIMULATING MESOLIMBIC AND NIGRO-STRIATAL DOPAMINERGIC PATHWAYS IN THE RAT

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SUMMARY: Mesolimbic and nigro-striatal dopamine systems were activated by injections of muscimol into the VTA and SNR respectively. The behavioural patterns produced (LMA, sniffing, rearing and grooming) were the same in each case. Clozapine, but not haloperidol, selectively antagonised the effects of VTA injected muscimol.

INTRODUCTION

Antipsychotic drugs have been divided into typical (e.g. haloperidol) and atypical compounds (e.g. clozapine) according to whether or not they cause extrapyramidal side effects (EPS) in man. The induction of EPS is thought to be due to a blockade of nigro-striatal dopamine systems, whereas the positive antipsychotic effect is regarded as a manifestation of the blockade of mesolimbic dopamine systems (Meltzer et al., 1989). In an effort to predict the potential antipsychotic and EPS-inducing ability of drugs we have developed behavioural models, that rely on selective stimulation of mesolimbic and nigro-striatal dopamine pathways. This has been achieved by direct central injections of the GABA-A agonist, muscimol, into either the ventral tegmental area (VTA) or the substantia nigra zona reticulata (SNR) of rats.

Muscimol injections into these regions have previously been reported to induce behavioural stimulation (Arnt & Scheel-Kruger, 1979; Scheel-Kruger et al., 1977). Due to the universal inhibitory nature of GABA, the stimulation induced by muscimol is
likely to be via an indirect mechanism, which is not inconsistent with the known neuroanatomy of the two regions (Fallon & Loughlin, 1985).

METHODS

Male Wistar-derived rats (AHA, 180-220g) were implanted with bilateral guide cannulae terminating 3 mm above the VTA (coordinates; AP -4.8, -5.3, Lat 1, D 8.5) or SNR (AP -4.8, -5.8, Lat 2.5, D 8.5, Paxinos & Watson, 1982).

After 7 days recovery, rats were injected bilaterally via a 30 gauge injection cannula advanced into the VTA or SNR with either vehicle (artificial CSF) or muscimol (10-200ng) in a volume of 0.5 ml over a period of 1 min. In all studies rats were placed in clear perspex solid bottomed cages, to which they had been allowed 30 min habituation, and observed for 30-40 min after muscimol administration. The following behaviours were scored for 2 min in every 10 min time period:- Locomotor activity (LMA) - line crossings/min Rearing - number/min Sniffing - Intensity (0-absent, 1-slight, 2-moderate, 3-intense) and bout duration (s) Grooming - intensity and bout duration as for sniffing.

For antagonist studies, rats were pretreated with haloperidol (0.01-0.25mg/kg i.p.) or clozapine (0.1-12.5mg/kg i.p.) 30 min before muscimol (100ng) administration. ED50 values were calculated using the method of Litchfield & Wilcoxon (1949). Rats were used no more than 3 times with at least 7 days being left between each testing. The locations of injection cannulae were verified histologically at the conclusion of each series of experiments.

RESULTS

Injections of muscimol into both the VTA and SNR produced dose-related increases in LMA (Fig. 1). Similar increases were seen in rearing behaviour (data not shown) and sniffing intensity (Fig. 1).

Bout duration of sniffing was also increased in a dose related fashion after VTA administration of muscimol (e.g. CSF 0.5 ± 0.4s, Musc. (30ng) 5.4 ± 1.0s, Musc. (200ng) 19.2 ± 3.2s), but not to the same degree after SNR administration (e.g. CSF 1.4 ± 0.7s, Musc. (30ng) 5.1 ± 0.7s, Musc. (200ng) 7.4 ± 2.3s). Grooming