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The effects of (+)-SKF10047 and ketamine hydrochloride on stereotyped behaviour, locomotor activity and ataxia in guinea pig

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Abstract

Although behavioural studies of the effects of (±)-*N*-allylnormetazocine ((+)-SKF10047) and ketamine hydrochloride have been conducted in many species, there are no data available on their effects in guinea pig. The aim of the present study was to provide an analysis of the effects of these drugs on stereotyped behaviour, locomotor activity, ataxia and righting reflex latency in guinea pigs. (+)-SKF10047 did not produce significant stereotyped behaviour nor locomotor hyperactivity at any of the doses tested (2.5–10.0 mg/kg, i.p). While righting reflex latency was not significantly affected, significant ataxia was produced at the highest (+)-SKF10047 dose used (i.e., 10 mg/kg). The results for ketamine hydrochloride were similar. Neither significant stereotyped behaviour nor locomotor hyperactivity were produced by ketamine at either dose used (12.5 and 25.0 mg/kg, i.p). However, at the lower dose (i.e., 12.5 mg/kg), significant ataxia and a significant impairment of the righting reflex were produced.

Keywords: (+)-SKF10047; Ketamine hydrochloride; σ Receptor; (Guinea pig)

1. Introduction

The σ receptor agonist, (±)-*N*-allylnormetazocine ((+)-SKF10047), and non-competitive NMDA receptor/channel antagonists, such as phencyclidine (PCP), and ketamine hydrochloride (Brady et al., 1982; McCann and Su, 1990; Olney et al., 1989; Zukin and Zukin, 1979), have been demonstrated to induce cognitive effects resembling psychosis and dementia in primates (e.g., Boyce et al., 1991; Brady et al., 1982; Chavkin, 1990; Lahti et al., 1995). As a consequence, attempts have been made to use the behavioural effects of such drugs as an animal model of psychosis in humans (e.g., Boyce et al., 1991; Brady et al., 1982; Contreras et al., 1986, 1988; Hiramatsu et al., 1987, 1989; Marquis et al., 1989; for reviews, see Chavkin, 1990; Ellison, 1995; Javitt and Zukin, 1991). These drugs have been reported to induce stereotyped behaviour and locomotor hyperactivity, which are often used as an indication of 'psychotic' behaviour, in lower mammalian species (e.g., Brady et al., 1982; Contreras et al., 1986, 1988; Hargreaves and Cain, 1995; Hiramatsu et al., 1987, 1989; Jerram et al., 1996; Marquis et al., 1989; Sturgeon et al., 1979); however, they also cause impairments of motor coordination which must be taken into account when interpreting the presence or absence of other behavioural effects (Carter, 1994).

Studies of the σ receptor have been confused by disagreement regarding its identity (Boyce et al., 1991; Chavkin, 1990). Attempts have been made to redefine the σ receptor and distinguish the non-opioid, non-PCP haloperidol-sensitive σ receptor from the naloxone-sensitive opioid σ receptor and the PCP site within the NMDA receptor ion channel (Chavkin, 1990). The σ receptor agonist, (+)-SKF10047, is believed to have a high affinity for the haloperidol-sensitive σ site; ketamine hydrochloride, by contrast, has a high affinity for the PCP site within the NMDA receptor ion channel (Chavkin, 1990).

In order to study the specific behavioural or neural effects of agonists for the haloperidol-sensitive σ site ('σ receptor agonists') and non-competitive NMDA receptor/channel antagonists, it is important to have a general description of the behavioural effects of these drugs in the

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species concerned. Although the behavioural effects of several of these drugs have been studied in rats (Brady et al., 1982; Contreras et al., 1986, 1988; Hiramatsu et al., 1989; Sanger and Jackson, 1989; Hiramatsu et al., 1987; Jones et al., 1990; Marquis et al., 1989; Sturgeon et al., 1979), mice (Carter, 1994), dogs (Vaupel, 1983), squirrel monkeys (Boyce et al., 1991; Brady et al., 1982), rhesus monkeys (Boyce et al., 1991) and humans (Lahti et al., 1995), to our knowledge there are no data available on their effects in guinea pigs. The primary aim of the present study was to examine the effects of (+)-SKF10047 and ketamine hydrochloride in guinea pigs, with a view to providing a foundation for further studies of these drugs in this species. In addition, the study had the objective of providing data for comparison with the effects of (+)-SKF10047 and ketamine in other species and for comparison with the effects of other, competitive, NMDA receptor antagonists in guinea pig (Jerram et al., 1996). (+)-SKF10047 and ketamine hydrochloride were chosen for this purpose because of the differences in their affinities for the haloperidol-sensitive σ binding site and the PCP site within the NMDA receptor ion channel, respectively (Chavkin, 1990).

2. Materials and methods

The subjects were 24 adult guinea pigs (280–406 g). They were housed in pairs in an animal holding room with a 12 h dark/12 h light cycle; food and water were available ad libitum. 1 day prior to the beginning of the experiment, the animals were brought into the laboratory, housed individually, and allowed to adjust to the laboratory conditions in which the experiment would take place. Each animal was then housed individually in the experimental observation box (see below) 1 h prior to the beginning of the experiment.

The animals were randomly divided into six groups: group 1 ($n = 4$) received 2.5 mg/kg (+)-SKF10047 (i.e., as the hydrochloride salt, RBI, New Jersey); group 2 ($n = 4$) 5.0 mg/kg (+)-SKF10047; group 3 ($n = 4$) 10.0 mg/kg (+)-SKF10047; group 4 ($n = 4$) 12.5 mg/kg ketamine hydrochloride (Parnell, New Zealand); group 5 ($n = 4$) 25.0 mg/kg ketamine hydrochloride; group 6 ($n = 4$) 1 ml/kg distilled water (vehicle control). In all cases the injection consisted of a 1 ml/kg volume of distilled water. The (+)-SKF10047 and ketamine hydrochloride doses were chosen on the basis of previous studies (Boyce et al., 1991; Hiramatsu et al., 1987; Jones et al., 1990; Vaupel, 1983). The sample size used ($n = 4$ per group) was based on variance estimates obtained in our previous study of the effects of NMDA receptor antagonists (Jerram et al., 1996). All measurements were made using a double-blind protocol: the vehicle and drug solutions were colour-coded such that neither the person injecting the solutions nor the person observing the animals and making the measurements knew which animals received particular drug doses and which received vehicle injections.

During testing, animals were placed in a large open box (61 × 61 × 22 cm) with a transparent Perspex front panel. In order to facilitate the behavioural measurements, animals were videotaped using two video cameras (Panasonic NV-M7), each with a zoom lens; one was positioned directly above the animal, the other in front of the Perspex window at the front of the box. The signals from the two cameras could be mixed using a Panasonic (Digital WJ-MX10) video mixer and were displayed on a Sony Trinitron color monitor using a split screen. Videotapes were replayed using a Mitsubishi E7 Black Diamond video recorder. Animals were videotaped for 20 min before the drug or vehicle injection and then for 155 min following the injection (Jerram et al., 1996). With the exception of groups 1 and 2 (i.e., 2.5 and 5.0 mg/kg (+)-SKF10047), four behavioural variables were measured for all animals: (1) stereotyped behaviour; (2) ataxia; (3) locomotor activity; and (4) righting reflex latency. For groups 1 and 2, ataxia was not quantified because it was clear from the initial studies that there was none. Stereotyped behaviour, ataxia and locomotor activity were measured using the Contreras et al. (1988) modification of the rating scale developed by Sturgeon et al. (1979) for the description of PCP-induced behaviours in rats; these measurements were made at 10 min intervals for 20 min before the injection and for 2.5 h following the injection. Righting reflex latency was measured using a custom-made electronic device consisting of a semicylindrical platform positioned on a 2 kg load cell. The load cell transduced changes in load during a righting reflex into a signal that was amplified and displayed as a waveform on a MacClassic computer screen via a MacLab data acquisition system (Analog Digital Instruments). The MacLab system sampled from the amplifier at 20 Hz, giving a measurement resolution of 0.05 s. The latency to generate a righting reflex could be measured using cursors in the Chart program (see Dingwall et al. (1993) for details). Righting reflex latency measurements were made once prior to the injection and at 30 min intervals thereafter for 2.5 h.

Data were analysed using 2-factor analyses of variance with repeated measures on time (Snedecor and Cochran, 1989). In all cases the significance rate was set at 0.05.

3. Results

(+)-SKF10047 did not produce significant stereotyped behaviour nor locomotor hyperactivity at any of the doses tested. While righting reflex latency was not significantly affected (Fig. 2A, B, C), significant ataxia was produced at the highest (+)-SKF10047 dose (i.e., 10 mg/kg; $P < 0.05$) (Fig. 1A).

The results for ketamine hydrochloride were similar.

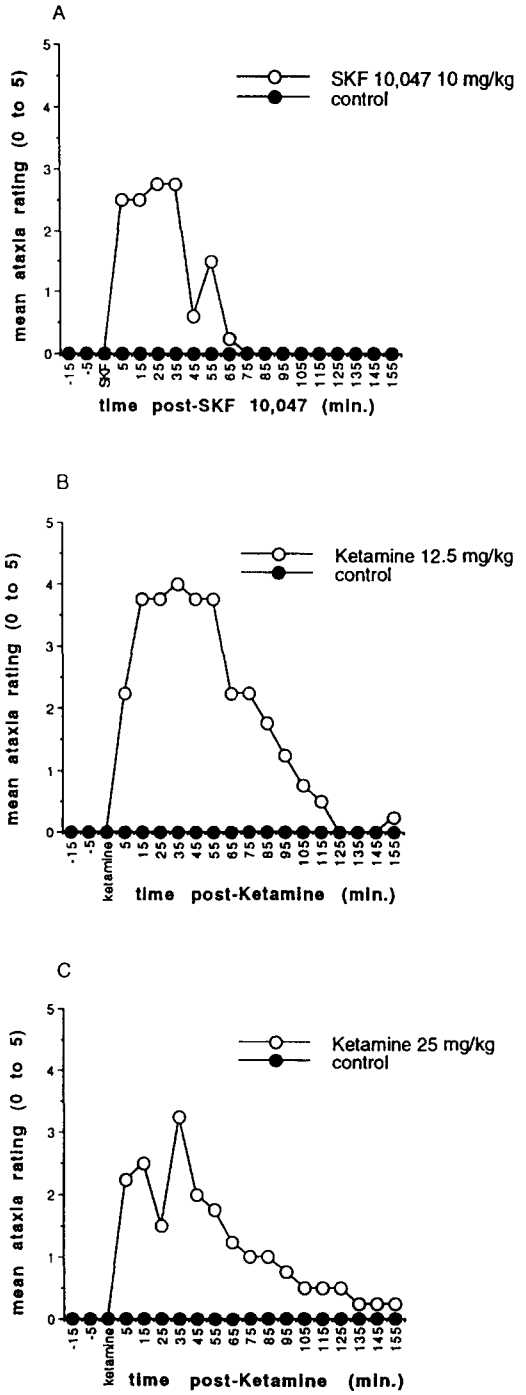

Fig. 1. Time course of ataxic effects of i.p. (+)-SKF10047 (A: 10.0 mg/kg) and i.p. ketamine hydrochloride (B: 12.5 mg/kg; C: 25.0 mg/kg). Symbols represent mean ratings (0–5). Open symbols: drug groups ($n = 4$). Closed symbols: vehicle controls ($n = 4$).

Neither significant stereotyped behaviour nor locomotor hyperactivity were produced by ketamine at either dose. However, at the lower dose (i.e., 12.5 mg/kg), significant ataxia($P < 0.01$) and a significant impairment of the righting reflex ($P < 0.05$) were produced (Fig. 1B, C, Fig. 2D, E, respectively).

4. Discussion

The results of the current experiment were surprising in view of the lack of stereotyped behaviour and locomotor hyperactivity produced by (+)-SKF10047 and ketamine hydrochloride. Previous studies in rats have reported that (+)-SKF10047 produced stereotyped behaviour in the dose ranges used in the current experiment (Brady et al., 1982; Contreras et al., 1986; Hiramatsu et al., 1987; Jones et al., 1990). However, some studies in primates and rats (Boyce et al., 1991; Jones et al., 1990) suggest that the ability to induce stereotyped behaviour is correlated with high affinity for the PCP site within the NMDA receptor complex rather than the haloperidol-sensitive σ receptor. Consequently, in squirrel monkeys and rhesus monkeys, (+)-SKF10047 was found to be less effective in producing stereotyped behaviour than the non-competitive NMDA receptor/channel antagonists, (+) − 5-methyl − 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten − 5,10-imine maleate (MK-801), and PCP (Boyce et al., 1991; Lodge and Johnson, 1990; McBain and Mayer, 1994). However, in the present study, ketamine hydrochloride did not produce stereotyped behaviour. Furthermore, in a previous study (Jerram et al., 1996) we found that neither (+)-MK-801 nor the competitive NMDA receptor antagonist, 3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) (Lodge and Johnson, 1990; McBain and Mayer, 1994), produced stereotyped behaviour and locomotor hyperactivity in guinea pig, although ataxia was frequently observed, as in the present study. These results suggest that neither drugs with high affinity for the haloperidol-sensitive σ site (e.g., (+)-SKF10047)), non-competitive NMDA receptor/channel antagonists with high affinity for the PCP site (e.g., ketamine hydrochloride, (+)-MK-801), nor competitive NMDA receptor antagonists (e.g., CPP), produce stereotyped behaviour in guinea pig.

It is unlikely that our methodology was responsible for the lack of stereotyped behaviour observed in the present study. Our use of a double-blind measurement protocol afforded additional experimental control in the application of the rating scales for stereotyped behaviour, ataxia and locomotor behaviour. One possible explanation of our data is that (+)-SKF10047 and ketamine produce their cognitive effects in guinea pigs only at high doses (e.g., > 10 mg/kg (+)-SKF10047), and at such doses the ataxic and sedative effects of the drug may obscure stereotyped behaviour and locomotor hyperactivity. However, it is unlikely that this is the complete explanation for the absence of stereotyped behaviour in guinea pig following injections of σ receptor agonists and non-competitive NMDA receptor/channel antagonists. First, although the higher ketamine dose used in the present study (i.e., 25.0 mg/kg) did not induce significant ataxia or impairment of the righting reflex, stereotyped behaviour and locomotor hyperactivity were still not observed. Second, in our previous study (Jerram et al., 1996) of competitive NMDA receptor

antagonists, high doses of CPP induced neither ataxia nor stereotyped behaviour.

There may be significant variability in the effects of σ receptor agonists and NMDA receptor antagonists between different mammalian species. It may be that the nature of stereotyped behaviour in guinea pig is fundamentally different to that in other species such as mouse, rat, pigeon, squirrel monkey and rhesus monkey. The rating scale that we used to quantify stereotyped behaviour was based on that used by Contreras et al. (1986, 1988) to rate PCP-induced behaviours in rats; therefore, it is possible that its application to guinea pigs was inappropriate. For example, it may be that in guinea pig, σ receptor agonists and NMDA receptor antagonists produce more type II, negative psychotic symptoms (i.e., withdrawal, flat affect) than in other species. However, at present, it is not clear how

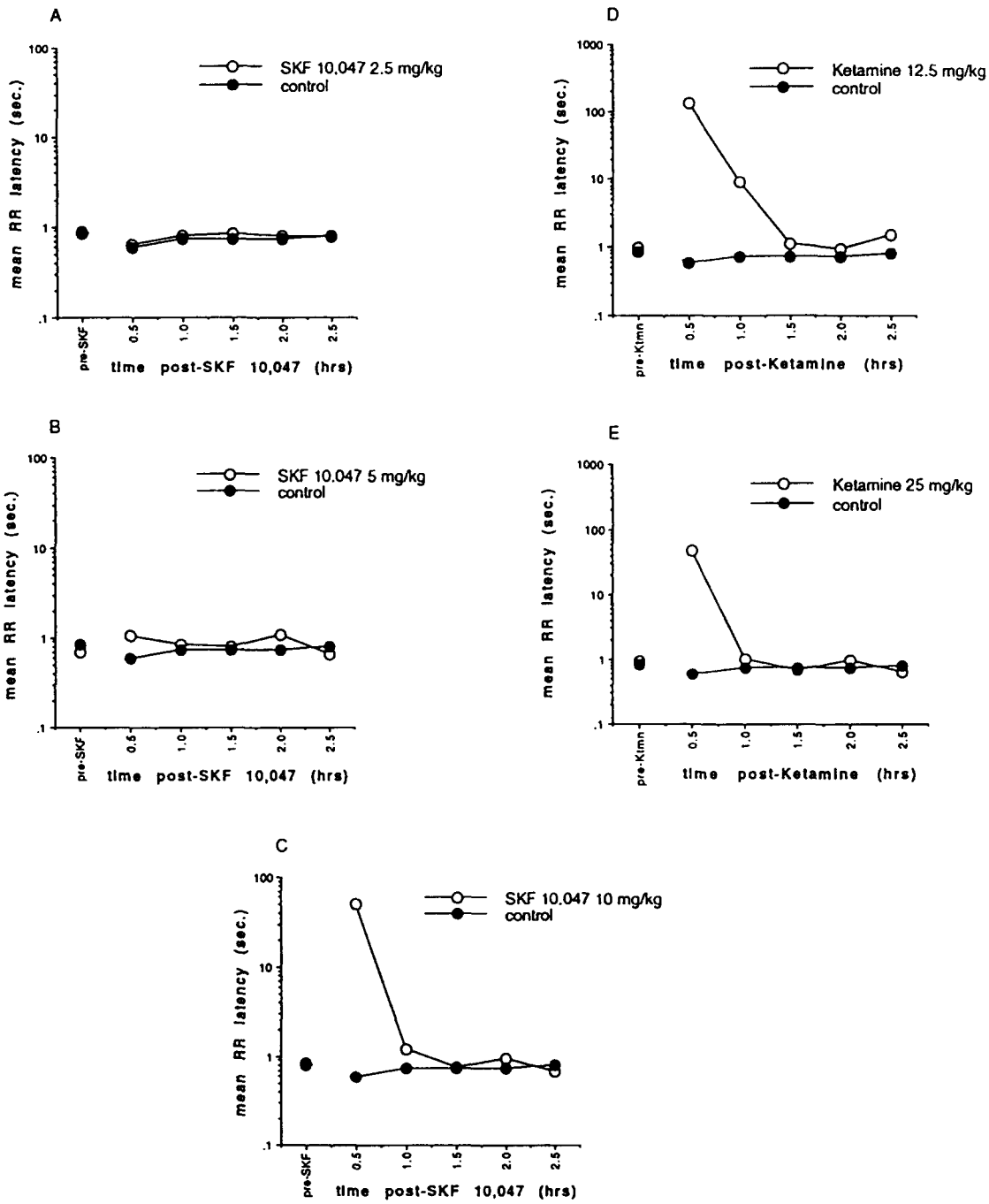

Fig. 2. Time course of effects of i.p. (+)-SKF10047 (A: 2.5 mg/kg; B: 5.0 mg/kg; C: 10.0 mg/kg) and i.p. ketamine hydrochloride (D: 12.5 mg/kg; E: 25.0 mg/kg) on righting reflex latency. Symbols represent latencies in seconds, expressed on a log scale. Open symbols: drug groups ($n = 4$). Closed symbols: vehicle controls ($n = 4$). RR: righting reflex. hrs: hours.

this hypothesis could be tested in guinea pigs, given that their behaviour is normally very limited compared to other species like rats and mice.

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