*Brain Research*, 526 (1990) 355–358
Elsevier



BRES 24265

# Analgesic, anesthetic, and respiratory effects of the competitive *N*-methyl-D-aspartate (NMDA) antagonist CGS 19755 in rhesus monkeys

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(Accepted 29 May 1990)

*Key words:* Rhesus monkey; Analgesia; Anesthesia; Respiration; CGS 19755; Excitatory amino acid antagonist

The competitive excitatory amino acid antagonist cis-4-phosphonomethyl-2-piperidine-carboxylic acid (CGS 19755) increased the latency for monkeys to remove their tails from warm water (analgesia); larger doses produced ataxia, loss of righting, salivation, and eliminated reactivity to stimulation (anesthesia). CGS 19755 decreased tidal volume and had little effect on frequency of respiration. Although longer lasting, the effects of CGS 19755 were similar to the effects of ketamine, suggesting these effects result from actions at the NMDA receptor complex.

Two classes of compounds have been shown to attenuate effects mediated through the *N*-methyl-D-aspartate (NMDA)-associated receptor complex: competitive NMDA receptor antagonists and ketamine-like compounds. CGS 19755 (cis-4-phosphonomethyl-2-piperidine-carboxylic acid), a systemically active, competitive antagonist at NMDA receptors[1,7,8], fails to produce ketamine-like discriminative stimulus effects in monkeys at doses that antagonize a behavioral effect of NMDA[5]. This finding raises the possibility that in humans competitive NMDA antagonists might not share subjective effects, including psychotomimetic effects, with ketamine-like compounds (e.g. phencyclidine).

Behavioral effects of ketamine-like compounds have been studied extensively in non-human primates. We recently reported[4] that, for a series of ketamine-like compounds, the potency to produce analgesic effects was correlated with the potency to produce ketamine-like discriminative stimulus effects and the potency to produce anesthesia, suggesting the NMDA-associated receptor complex might be involved in both the analgesic and anesthetic effects of ketamine-like compounds.

Direct effects of competitive NMDA antagonists have not been studied extensively although there is a report showing the competitive antagonist 2-amino-5-phosphonovalerate (AP5) produces ketamine-like anesthesia after i.c.v. administration in monkeys[10]. The present study reports on the analgesic, anesthetic, and respiratory effects of systemically administered CGS 19755 in rhesus monkeys.

Seven adult (6–10 kg) rhesus monkeys (*Macaca mulatta*) were housed individually with free access to Purina Monkey Chow and water. Two monkeys were prepared with chronic indwelling i.v. catheters.

Analgesic effects of CGS 19755 were studied using a warm water tail withdrawal procedure[2]. Three subjects received s.c. injections of 3.2, 10.0, or 32.0 mg/kg of CGS 19755 and the latencies were recorded for monkeys to remove their tails from a thermos containing 40, 50 or 55 °C water. If a subject did not remove its tail within 20 s the experimenter removed the thermos and scored a 20-s latency for that cycle. The 3 temperatures were presented in a non-systematic order every 30 min for 5.5 h or until withdrawal latencies returned to predrug values. Tail withdrawal latencies were also determined 12 and 24 h after administration of the larger doses of CGS 19755.

A video recording was used to score two subjects for the presence or absence of ataxia, loss of righting, salivation, and eye closure after i.v. infusion of 56.0 or 100.0 mg/kg of CGS 19755. Trained observers also rated monkeys for muscle relaxation and reactivity to stimulation (pin pricks over the body surface).

The effects of s.c. injections of 1.0, 3.2, 10.0, 32.0 or 56.0 mg/kg of CGS 19755 were studied in two monkeys breathing air or 5% $CO_2$ in air[6]. Normal air or 5% $CO_2$ in air was delivered (10 l/min) into a sealed helmet placed over the subject's head; changes in pressure, measured and recorded by a transducer and a microprocessor, were transformed to frequency of respiration ($f$) in breaths/min

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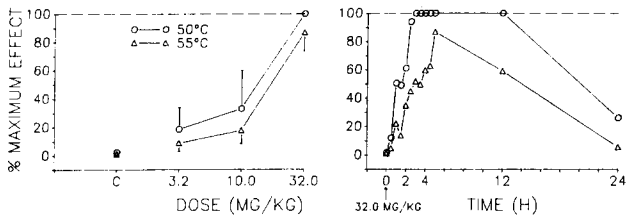


Fig. 1. Dose–effect curves for the effects of CGS 19755 on the latency for monkeys to remove their tails from warm water (left panel) and time-course for the same effects produced by a single injection of 32.0 mg/kg of CGS 19755 (right panel). Ordinate: left panel, maximum averaged latency (± 1 S.E.M.) observed for each dose during a 5.5 h experiment and expressed as a mean percentage of the maximum possible effect (i.e. [(test latency–control latency)/ 20–control latency] × 100); right panel, average latency for single determinations in each of 3 monkeys. Abscissae: left panel, control (C; no drug) or dose of CGS 19755 in mg/kg b. wt. administered s.c.; right panel, time (h) after administration of 32.0 mg/kg of CGS 19755. Because monkeys reliably had withdrawal latencies of 18 s or longer for 40 °C water both before and after drug administration, only results with 50 and 55 °C are presented.

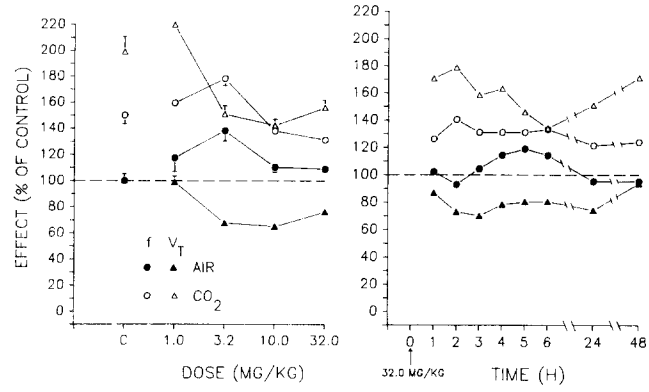


Fig. 2. Dose–effect curves (left panel) and time course (right panel) for the effects of CGS 19755 on $f$ and $V_T$ in air and in 5% $CO_2$ in air for monkey TE. Ordinates: $f$ and $V_T$ expressed as a percentage of $f$ and $V_T$ under control (i.e. no drug, air) conditions. Abscissae: left panel, control (C; no drug) or dose of CGS 19755 in mg/kg b. wt. administered s.c. (except for points above C which are averages of 8 3-min observations determined prior to drug administration, each point is the mean ± 1 S.E.M. of 10 3-min observations obtained every 30 min beginning 1 h after drug administration); right panel, time (h) after administration of 32.0 mg/kg of CGS 19755 (each point is the average of 2 3-min observations).

and tidal volume ($V_T$) in ml/inspiration. Data were recorded continuously; 23-min exposures to air alternated with 7-min exposures to $CO_2$. The last 3 min of exposure to $CO_2$ were used for data analyses and were compared to the last 3 min during the air only component. Drug was administered during the first min of the second 23-min exposure to air and observations continued for up to 6 h. In addition, monkeys were studied daily for up to 4 days after administration of large doses of CGS 19755.

Under control (no drug) conditions the average latencies for monkeys to remove their tails from 50 and 55 °C water were 2.3 ± 0.8 and 1.0 ± 0.1 s, respectively. CGS 19755 increased the latency for monkeys to remove their tails from warm water (Fig. 1). A dose of 3.2 mg/kg of CGS 19755 produced a small increase in withdrawal latencies, whereas a dose of 10.0 mg/kg increased latencies to 33% and 17% of the maximum possible effect for 50 and 55 °C, respectively. Maximum effects obtained with 3.2 and 10.0 mg/kg of CGS 19755 occurred 1.5–3 h after drug administration with latencies near control values 5 h after drug injection (data not shown). Maximum effects obtained with 32.0 mg/kg (100% and 86% for 50 and 55 °C water, respectively) occurred 2.5–5.5 h after drug administration (right panel, Fig. 1); the effects with 55 °C water were decreased to 60% of the maximum 12 h after drug injection and effects with both temperatures were reduced markedly by 24 h. CGS 19755, at a dose of 32.0 mg/kg, also produced ataxia and profuse salivation. Due to the marked ataxia, loss of righting, and salivation observed with 56.0 mg/kg in other subjects larger doses of CGS 19755 were not studied in the tail withdrawal procedure.

Monkeys showed ataxia 30–45 min following i.v. administration of 56.0 mg/kg of CGS 19755. Postural effects increased through time and were accompanied by salivation and a lack of responsiveness to stimulation. Two h after administration of 100.0 mg/kg of CGS 19755 both monkeys were lying on their sides and neither subject responded to pinch or to pin pricks. Although ataxic and generally immobile, there was no eye closure, muscle tone was present, and there was occasional limb movement. Anesthesia persisted for over 12 h after administration of 100.0 mg/kg and gradually subsided to ataxia by 24 h after drug administration.

Under control (no drug) conditions, respiratory measures (means ± 1 S.E.M.) for the two monkeys were: $f$ = 20.0 ± 0.7, $V_T$ = 155.5 ± 6.2 in air; and $f$ = 30.0 ± 1.3, $V_T$ = 229.5 ± 14.0 in 5% $CO_2$ for subject TE; $f$ = 21.3 ± 0.8, $V_T$ = 108.0 ± 7.8 in air; and $f$ = 25.8 ± 0.9, $V_T$ = 177.2 ± 11.8 in 5% $CO_2$ for subject SA. Thus, 5% $CO_2$ increased $f$ to 120–150% of control and $V_T$ to 164–198% of control.

CGS 19755 decreased $V_T$ in air and in $CO_2$ (Fig. 2). A dose of 1.0 mg/kg of CGS 19755 had no effect on $V_T$ in air and increased $V_T$ slightly in $CO_2$. A dose of 3.2 mg/kg CGS 19755 decreased $V_T$ in air to 67% of control and decreased $V_T$ in $CO_2$ to 150% of control (decrease of 24% compared to $V_T$ in $CO_2$ with no drug); there was a concomitant 18–38% increase in $f$ both in air and in $CO_2$. Increasing the dose of CGS 19755 to 10.0 or 32.0 mg/kg did not further decrease $V_T$ compared to results obtained with 3.2 mg/kg; moreover, increases in $f$ observed with

3.2 mg/kg of CGS 19755 were not evident with larger doses.

The time course of effects of 32.0 mg/kg of CGS 19755 is shown in the right panel of Fig. 2. This dose produced a modest, sustained decrease in $V_T$ with maximum decreases to 69% of control in air and 134% of control in $CO_2$ occurring 2.5–6 h after drug administration. This dose had no effect on $f$ in $CO_2$ and produced a small increase in $f$ in air. Twenty-four h after 32.0 mg/kg of CGS 19755 $V_T$ was still suppressed (74% of control in air and 151% of control in $CO_2$); by 48 h postinjection $V_T$ in air and in $CO_2$ had returned to near control values.

Results obtained in monkey SA (data not shown) were qualitatively the same as results shown in Fig. 2. A dose of 56.0 mg/kg of CGS 19755 was studied only in monkey SA; 3 h after injection of 56.0 mg/kg $V_T$ was decreased in air and in $CO_2$ to less than 50% of control. Although there was no effect on $f$ in air or in $CO_2$ over the same time course, 3.5 h after administration of 56.0 mg/kg, $f$ in $CO_2$ decreased rapidly to 73% of control (40% decrease compared to $f$ in $CO_2$ with no drug). Large decreases in $V_T$ and $f$ were accompanied by anesthesia and profuse salivation that required termination of the experiment. This monkey remained anesthetized for more than 12 h and ataxic for more than 24 h; 52 and 70 h after receiving 56.0 mg/kg of CGS 19755 the subject appeared normal although both $V_T$ and $f$ were decreased by as much as 30%. Respiratory function was normal 102 h after administration of 56.0 mg/kg of CGS 19755.

At doses that did not produce observable behavioral effects CGS 19755 increased the latency for monkeys to remove their tails from warm water. Larger doses of CGS 19755 produced ataxia, loss of righting, nystagmus, salivation, and diminished or eliminated reactivity to stimulation without producing eye closure or muscle relaxation. Doses of CGS 19755 required to produce behavioral effects in the current study were 3–30 times larger than doses that attenuate effects of NMDA under other conditions[1,5,8], suggesting greater receptor occupancy is required to exert direct behavioral effects than to antagonize the effects of exogenously administered agonists. The effects of CGS 19755 were qualitatively the same as effects of ketamine-like compounds as well as the competitive NMDA antagonist AP5[10] and the relative potency between analgesic and anesthetic effects (3-fold) for CGS 19755 was comparable to that observed for several ketamine-like compounds[4]. The similarity in anesthetic effects produced by competitive NMDA antagonists and ketamine-like compounds supports the proposition that the anesthetic effects of both classes of compounds occur because of actions at the NMDA receptor complex.

Ketamine has only modest effects on respiration in non-human primates, up to doses that produce anesthesia[9], and it is not clear whether the lethal respiratory effects reported for the competitive NMDA antagonist AP5[10] were the result of actions at an NMDA receptor complex. Moderate decreases in $V_T$ and small increases in $f$ obtained with CGS 19755 in the present study parallel the effects of ketamine in monkeys (unpublished observation) and support the notion that neurotransmission at the NMDA receptor complex is important in the control of respiratory function[3].

As compared to ketamine, the onset of analgesic and anesthetic effects was relatively slow for CGS 19755; effects were not evident until 30–45 min after i.v. infusion and, at doses that altered respiration for several days, the effects of CGS 19755 were not manifest until 2–3 h after s.c. administration. Once established, however, the effects of CGS 19755 persisted for 24 h or longer. The slow onset and long duration of action for analgesic, anesthetic, and respiratory effects are in contrast to the rapid onset and short duration of action reported for other effects of CGS 19755. For example, within 45 min of s.c. administration, small doses of CGS 19755 (0.1–3.2 mg/kg) attenuate the rate-decreasing effects of NMDA in monkeys and this attenuation is markedly diminished at 2 h and almost absent 24 h after drug injection[5]. In mice the anticonvulsant effects of CGS 19755 peak at 1 h ($ED_{50}$ = 2.1 mg/kg) and are markedly reduced by 4 h ($ED_{50}$ = 16.5 mg/kg) after i.p. administration[1]. Competitive NMDA antagonists have not been studied extensively in vivo, however, results obtained to date indicate two profiles of behavioral action for CGS 19755: rapid onset, short duration effects (e.g. anticonvulsant effects); slow onset, long duration effects (e.g. anesthetic effects). Whether these differences represent pharmacokinetic factors or multiple mechanisms of action (e.g. different receptor types) for CGS 19755 remains to be determined.

The long duration of action for some effects of CGS 19755 might preclude applications to conditions in which ketamine is currently used (e.g. analgesia-anesthesia in burn patients), however, a short-acting competitive antagonist might be a useful anesthetic. A problem associated with the clinical use of ketamine is the hallucinatory-dysphoric state that sometimes occurs upon emergence from anesthesia; if competitive antagonists do not share this effect with ketamine, as suggested by drug discrimination studies in monkeys[5], these compounds might be an interesting new class of anesthetics.

We would like to thank CIBA-Geigy (Summit, NJ) for CGS 19755, A. Yung for technical assistance, and L. LaCross and R. McLaughlin for assistance in preparing the manuscript. This research supported by USPHS Grants DA05325 and DA00254.

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