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Cesium Attenuates Conditioned Avoidance Response in Rats and Mice

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BOSE, R. AND C. PINSKY. *Cesium attenuates conditioned avoidance response in rats and mice.* PHARMACOL BIOCHEM BEHAV **18**(6) 867–871, 1983.—The pole-climbing conditioned avoidance response (CAR) was attenuated in rats after four once-daily injections of CsCl intraperitoneally at 3.0 mEq kg^{-1} and in mice after seven such injections at 5.0 mEq kg^{-1}. Suppression of CAR increased with increasing numbers of injections. Treatment with cesium did not attenuate the unconditioned pole-climbing escape response to mild footshock. The cesium effect on CAR resembles that of antidopaminergic phenothiazinelike agents, in concordance with our earlier studies which showed cesium potentiation of pentobarbital sleeping time and antagonism of amphetamine toxicity.

Cesium CAR attenuation Pole-climbing CAR CAR-rats CAR-mice Cesium ion
Conditioned avoidance Cesium central actions Cesium readministration Antidopaminergic
Phenothiazinelike CAR response time Alkali metal ion

THERE is a variety of reports concerning the central nervous system (CNS) effects of the alkali-earth metal ion, cesium (Cs) [2, 14, 21, 23, 28, 29, 32]. Some investigators [21, 23, 28, 32] have described excitatory effects while others [2, 14, 29] have reported responses which suggested some degree of CNS depression, inhibition or no effect following long-term administration of low doses. Bose, Pinsky and co-workers found that repeated administration of CsCl, 1.25 to 20.0 mEq kg^{-1} intraperitoneally, induced hypoactivity in unrestrained mice, as evidenced by reduction in totalized motor behavioral events of horizontal movements, vertical activity ("rearing-up"), grooming, sniffing and teeth chatter ([2, 3, 29] Pinsky and Bose, unpublished). Similar treatment with CsCl potentiated pentobarbital sleeping time in mice [4]. Amphetamine aggregation toxicity [8,26] also was seen to be reduced in mice with such administration of cesium [4]. In contrast, cutaneospinal reflexes involved in morphine-induced antinociception in mice, and EEG patterns in rats, were unaffected by repeated administration of CsCl [4,29]. The cesium-induced behavioral hypoactivity was not accompanied by any impairment of the righting reflex over the specified dose range and there was no overt loss of motor ability nor of responsivity to stimuli such as handling and mild prodding ([4,29] Pinsky and Bose, unpublished). This pattern of effects suggested to us that cesium-induced reduction of ongoing motor behavior is not merely the expression of a generalized depressant effect of cesium ion on neuronal excitability. It appeared, instead, that the cesium ion may exert a specific neuroactivity similar to antipsychotic agents such as the phenothiazines and butyrophenones which are known to impair amphetamine aggregation toxicity [8, 16, 26] and to act on other correlational models in animals and man or on states of psychosis in patients [1, 10, 18, 20]. We have therefore examined the effects of cesium on the pole-climbing conditioned avoidance response (CAR) [11] in rats and mice, since that response also is blocked by phenothiazinelike antipsychotic drugs and is frequently used as a predictive drug screen to discern substances which may display antipsychotic effects in humans.

METHOD

Animals and Procedure Times

All test animals (supplier: Canadian Breeding Laboratories, St. Constant, PQ) were housed in temperature-controlled (21°C) and humidity-supplemented quarters, on a 6:00 a.m.–6:00 p.m. light, 6:00 p.m.–6:00 a.m. dark schedule. Animals were acclimatized to their quarters and to normal handling for at least three days after shipment before training was begun. They were housed in standard animal-house plastic cages of 12 l volume with wood shaving bedding for rats and of 6.2 l volume with sawdust bedding for mice. Male Sprague-Dawley albino rats weighing 80–100 g were in groups of five; male Swiss-Webster mice 18–20 g, in groups of ten. All injections, training and CAR experiments were done between 9:30 a.m. and 3:30 p.m.

Training Enclosures and Configuration

Rats. These were trained and tested in a cubic enclosure 45 cm on edge with clear acrylic walls and a removable acrylic top lid fitted at its centre with a wooden pole 40 cm length × 13 mm dia. projecting inward to the enclosure. The enclosure floor consisted of parallel stainless steel rods 3 mm dia. with centres spaced 10 mm apart. Alternate rods were electrically strapped, thus forming a grid through which electric current ("footshock") could be delivered to the rat's

underpaws regardless of the animal's stance while standing or crouching on the grid.

Mice. These were trained and tested in a transparent circular acrylic enclosure, 30×30 cm dia. × ht. The circular configuration reduced corner-seeking behavior and thus appeared to reduce the time taken by this species to approach the pole and learn to climb it. The floor of this enclosure was similar to that for rats, but with thinner rods of 2 mm dia. and with 7 mm spacing. The top lid held at its centre an inward-projecting wooden pole, 27 cm long × 9 mm dia.

Stimuli Used for CAR Studies

The conditioning stimulus was provided by a standard annuciator buzzer (Edwards, 725), sounding on the wooden table-top which held the acrylic enclosures and electric-grid floor. The sound level in the centre of the acrylic enclosures at the level of the animal's head was 72 dB above 10^{-16} W cm^{-2} as measured with a calibrated commercial sound level meter (Realistic) with standards traceable to audio-engineering industry specifications. The sound level was essentially nondirectional, displayed no corner or edge effects and varied less than ±2 dB over the middle 80% volume of either enclosure.

The unconditioned stimulus consisted of 60-Hz sinusoidal current from a constant-current source (output current not affected by changes in the body resistance of the animal). The delivered current could be chosen by the experimenter over the range of 0.0 to 0.8 mA, the latter having been found in a preliminary experiments to be maximal (see Results section). A reliable working stimulus current intensity, below maximal and above threshold (usually, 2 × threshold) for the unconditioned escape response (UER; escape represented by pole-climbing), was determined for each animal during CAR training procedures. Footshock intensity was not altered from the working values for individual animals during the drug studies which followed the CAR procedures.

CAR Training Schedule

Rats and mice. Each CAR trial consisted of the presentation of a 15-sec conditioning stimulus (buzzer sounding) followed by a 5-sec pause and thereafter by the unconditioned stimulus (footshock) lasting for 10 sec. The animal could readily avoid footshock by climbing the pole which projected into the enclosure. A successful response (CAR) was considered to have been achieved each time the animal climbed the pole after the buzzer sound had begun but before the unconditioned stimulus was applied. Each animal was subjected to 10 trials daily until it responded to the conditioning stimulus in 10 consecutive trials by climbing the pole at every buzzer sounding and without application of footshock (100% CAR response). Their responses were then reinforced ten times daily for two more days, three days apart. Reinforcement was by presentation of buzzer sounding followed, when necessary, by footshock. Most of the animals could thus be fully trained within 10–14 days; those which lagged behind at that stage were removed from the study. The latter procedure helped maintain inter-animal homogeneity in acquisition of training and eliminated the development of secondary CAR (pole-climbing prior to buzzer sounding, [18]). As well, it protected the rejected animals from a futile exposure to numerous episodes of footshock.

Pretraining of pole-climbing in mice. Before CAR training was begun in this species, the mice were trained to climb the pole in response to the unconditioned footshock stimulus. This pretraining lasted for 6–8 days, and was hastened by manually presenting the pole to the animal just prior and then subsequent to presentation of the footshock.

Cesium Treatments

Duration of treatment in rats and mice. Total durations of cesium treatments in rats (7 days) and in mice (14 days) were chosen from preliminary experiments [2,29] which showed significant behavioral responses with minimal signs of toxicity and low mortality after such treatments. The same durations of treatment resulted also in a significant uptake of cesium in the brains of rats and mice [30].

Injection procedures. (1) Rats: Cesium chloride (BDH, "Analar" grade) was dissolved in normal saline and injected intraperitoneally (IP) in volumes of 2.0 $\mu l\ g^{-1}$ body weight at a dose of 3.0 mEq kg^{-1}, once a day for 7 days beginning 24 hr after the final CAR training session. The control rats received injections of normal saline IP in equal volumes per body weight over the same period. (2) Mice: Cesium chloride was dissolved in normal saline and injected IP in volumes of 10.0 $\mu l\ g^{-1}$ body weight at a dose of 5.0 mEq kg^{-1}, once daily for 14 days beginning 24 hr after the final CAR training session. The control mice received injections of normal saline IP in equal volumes per body weight over the same period.

Determination of Cesium Effect on CAR and on the Unconditioned Escape Response (UER)

Rats. These were tested for CAR performance one hour after their 4th and 7th injections of cesium chloride or saline. The first animal to be tested on each experimental day was chosen at random from the cesium or saline groups, the rest were taken alternately from the two groups. This latter procedure was aimed at minimizing possible diurnal variation in responsivity. Two parameters of performance were measured: (1) Response time, which has been shown to be a sensitive variable in CAR performance [22]. This was estimated as the time elapsing from the initiation of buzzer sounding until the rat climbed on the pole; it was assigned a value of 15 sec ("cutoff") if the rat had failed to exhibit the CAR by then. (2) Proportion of successful responses in five consecutive CAR trials. Rats failing to show CAR were given footshock, 5 sec after end of buzzer sounding, to test for the presence of UER.

Mice. These were tested for CAR performance, one hour after their 7th and 14th injections of cesium chloride or saline. All other experimental procedures were as for those with rats. In testing CAR performance on the days specified (i.e., just prior to (i.e., control values), at the midpoint and at the end of an effective series of injections), an estimate was gained of the graded effects of duration of cesium treatment on CAR responses.

RESULTS

Training Procedures

The mean threshold values of footshock current to elicit the UER were similar in rats and mice, at approximately 0.2 mA. Training to 100% CAR success was accomplished in most animals with twice this value, which was almost exclusively utilized throughout this study. Animals that persistently required greater than 0.8 mA footshock intensity to produce the UER were not used in these experiments. Within

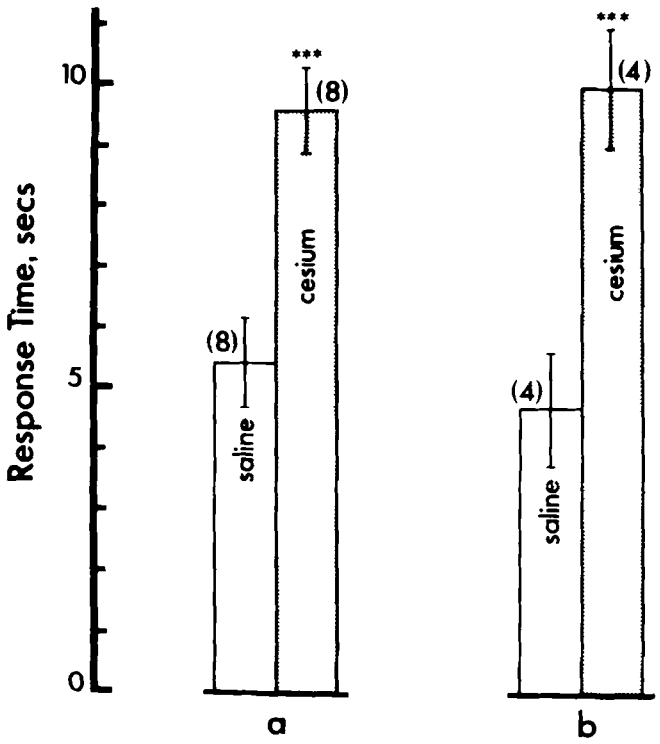

FIG. 1. Effect of cesium on CAR response time in rats. a=after 4 injections CsCl, 3.0 mEq Kg $^{-1}$ day $^{-1}$ IP; saline, 2.0 μl g^{-1} day^{-1} IP. b=after 7 injections, daily doses as in a. Significantly different from corresponding saline control group, $p<0.001$ (unpaired t-test). Numbers in parentheses indicate number of rats in each group.

this range of intensities the animals seldom showed signs of distress or overexcitement, as judged from an almost complete absence of vocalization, lack of aggressiveness or resistance to handling upon repeated placement in the training enclosure, and an only minimal increase in defecation and urination as compared by visual observation (counting boli and stains) to animals in the same enclosure without footshock. Mice acquired the pole-climbing CAR with roughly the same time and experimental effort given to rats in this study. None of the animals ever assumed any stance or posture which prevented them from receiving footshock, either during training or during the drug studies thereafter.

General Responses to Cesium Treatment

Repeated administration of CsCl, given to rats and mice according to the regimens described here, produced no signs of generalized toxicity. Spontaneous motor behavior was diminished, as previously described [2,29], but motor hypoactivity became less pronounced with prolonged administration of cesium and was not seen to interfere with pole-climbing ability in the experimental animals. There was no impairment of gait, posture or sensory ability, nor any significant mortality, all as compared with saline controls. With footshock intensities between 0.2 and 0.8 mA the UER was prompt and vigorous in all rats and mice during training, including those which exhibited failure of CAR. Pole-climbing was observed without exception during the first few seconds of footshock stimulus, as was the case also for animals in the control groups.

TABLE 1

EFFECTS OF CESIUM ION ON CONDITIONED AVOIDANCE RESPONDING IN RATS

Treatment × No. of injections IP	N	Total trials	Successful avoidance responses	p
Saline × 4	8	40	39	
CsCl 3.0 mEq kg^{-1} × 4	8	40	31	<0.02*
Saline × 7	4	20	19	
CsCl 3.0 mEq kg^{-1} × 7	4	20	16	†

*Different from concurrent saline controls (chi-square).
†No significant difference from concurrent controls.

Effects of Cesium on CAR in Rats

CAR response time. Mean response times (buzzer sounding—pole-climbing latency) for the cesium-treated rats with four daily injections of CsCl was 180% of that in saline controls, with seven injections it was 210% of the corresponding mean control values (Fig. 1). The differences were highly significant ($p<0.001$) even with only four rats per group. The increased response time seemed not to be an extinction [1] phenomenon related to time elapsed after the final training session, since mean latencies in the saline control groups were almost identical after four and seven days of injection (Fig. 1).

Proportion of responses. The CAR was elicited in 39 of 40 trials in eight control rats given four daily injections of saline after CAR training to the 100% response level (Table 1). CAR was elicited in only 31 of 40 trials in eight cesium-treated rats correspondingly given 4 daily injections of CsCl at 3.0 mEq kg^{-1}; this difference was significant with $p<0.02$ (Table 1). Four rats each from the same groups given 7 injections showed similar differences in proportions of responding, but not to a statistically significant level (Table 1). This loss of statistical inference may have been due to the reduced number of animals tested with 7 injections, this resulting from removal of eight rats for estimation of brain and peripheral organ levels of Cs by the method of proton-induced X-ray emission (PIXE) [24, 27, 31, 39] as reported elsewhere by Pinsky *et al.* [30].

Effects of Cesium on CAR in Mice

Mean CAR response times in cesium-treated groups with 7 and 14 injections were significantly higher than in saline control animals ($p<0.001$, Fig. 2). The CAR was elicited in all of 45 trials in 9 control mice injected once daily with saline for seven days, and in all of 40 trials in eight control mice so treated for 14 days (Table 2). There were 46 responses out of 75 trials in 15 mice injected daily with CsCl 5.0 mEq kg^{-1} for seven days and only 17 responses in 45 trials with nine mice so treated with CsCl for 14 days. Differences in these proportions between saline- and cesium-treated groups at each level of treatment were highly significant ($p<0.001$, Table 2). Furthermore, the effect with 14 injections of CsCl was significantly greater than with 7 injections, both in response time ($p<0.001$, Fig. 2) and in proportion of successful responses ($p<0.02$, Table 2). All animals showing failure of avoidance response invariably exhibited presence of intact escape response (UER) to footshock.

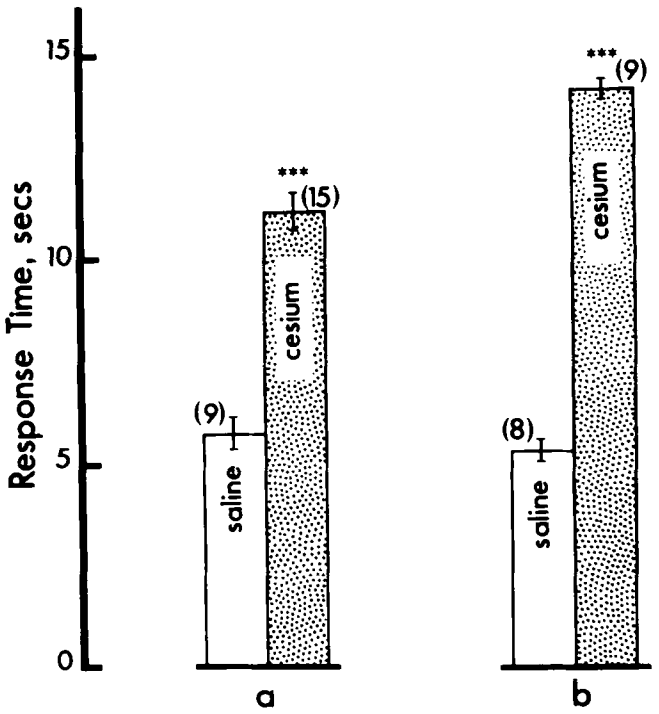

FIG. 2. Effect of cesium on CAR response time in mice. a=after 7 injections CsCl, 5.0 mEq Kg^{-1} day^{-1} IP; saline, 10.0 μl g^{-1} day^{-1} IP. b=after 14 injections, daily doses as in a. Significantly different from corresponding saline control group, $p<0.001$ (unpaired t-test). Numbers in parentheses indicate number of mice in each group.

TABLE 2

EFFECTS OF CESIUM ION ON CONDITIONED AVOIDANCE RESPONDING IN MICE

Treatment × No. of injections IP	N	Total trials	Successful avoidance responses	p
Saline × 7	9	45	45	
CsCl 5.0 mEq kg^{-1} × 7	15	75	46	<0.001*
Saline × 14	8	40	40	
CsCl × 14	9	45	17	<0.001*

*Different from concurrent saline controls (chi-square).

DISCUSSION

The effect of repeated administration of CsCl on CAR performance in rats and mice resembles that of phenothiazines [11, 13, 20] and other antipsychotic agents [15, 17, 18, 20] tested on the same paradigm. Much evidence is available from studies which range from clinical observations, behavioral pharmacology in animals and from studies at the molecular level, to implicate the dopamine receptor and dopaminergic neurotransmission in schizophrenia and other psychotic disorders [6, 7, 11, 16, 19, 20, 33–36, 38]. There is also a large body of parallel evidence to show that the therapeutic effectiveness of antipsychotic drugs is primarily due to their receptor blocking activity at central dopaminergic synapses [6, 12, 19, 20, 33–36, 38]. This places some central dopaminergic system as a prime candidate among various putative targets for the central action of cesium in our experiments. In a recent study in rats [32] CsCl (2.0 mEq kg^{-1} day^{-1} IP × 10 days) was shown to cause regional increases in brain dopamine content, with pons-medulla > hypothalamus > striatum > midbrain. There was a significant reduction in striatal content of homovanillic acid, the prime metabolite of dopamine. Such results suggest a possible inhibition of dopamine release from the corresponding neurons, resulting in reduced dopaminergic activity. This could account for the similarity of cesium action, as described in this report, with that established for dopamine antagonists on the CAR. It is of interest also that substances (e.g., morphine) which act at central dopaminergic synapses are known to exert biphasic effects on locomotor activity and behavior, subject to dosage regimen and duration of treatment [5,25]. This may in part explain divergences between those studies which have reported either excitant [21, 23, 28, 32] or depressant [2, 14, 29] behavioral effects with repeated administration of cesium.

The CAR paradigm has been demonstrated as the most specific among all animal behavioral models utilized in screening of drugs for antipsychotic properties [1, 7, 9–11, 20, 37]. Our present data suggest a cesium-induced suppression of a specific central mechanism rather than a generalized CNS depressant effect. The CAR was significantly suppressed with doses of CsCl which did not impair the unconditioned escape response. A similar trend has been shown in studies on the effects of cesium on shock-induced aggression in rats [14] and on aggregation toxicity in mice [4]. Cesium ion has no peripheral analgesic effect in the tail-flick test [4,29], hence the cesium-induced attenuation of the CAR observed in this study could not have been the result of an increased threshold to footshock pain. Such findings distinguish the action of cesium on the CAR from that of sedative-hypnotic agents, which obtund the CAR only at doses which also impair the escape response [9, 11, 18] and from analgesic agents which, unlike cesium [29], would be active in the tail-flick test. Demonstration of CAR sensitivity to cesium in both rats and mice shows that the phenomenon is not merely species-specific.

Mean levels of cesium in brains from the rats sampled 24 hr after injection of day 7 were found, in a separate study [30], to be 3.80±0.41 (mean±SE) mEq Cs^+ kg^{-1}. No grossly visible signs of brain toxicity (e.g., edema, shrinkage) were observed upon dissection. In other studies with mice, brain-to-body weight ratios were almost identical in saline- and cesium-treated groups over the entire course of 56 daily injections with saline or CsCl solutions given at the same dosage as used here [30]. It is therefore reasonable to suppose that the neuroactivity of cesium observed here was not due to cytotoxic effects on either neurons or glia.

Hence, there is a distinct pharmacological profile in the neuroactivity of cesium ion, shown by the selective suppression of an avoidance response known to be almost specifically sensitive to phenothiazinelike, antidopaminergic, antipsychotic agents. It might therefore be worthwhile to study the interaction of this ion with phenothiazines, and with other neuroleptic agents, whose clinical use in the high doses ncecessary for their therapeutic efficacy is associated with numerous short- and long-term side effects. Cesium, in

the dosages used here, did not appear to exert any cytotoxic effects on several major organ systems in rats and mice [30]. Its possible medical role in the enhancement of therapeutic efficacy of phenothiazinelike drugs without increasing the side effects of the latter might therefore be usefully investigated.

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