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ANTI-DEPRESSANT ACTION OF CAESIUM CHLORIDE AND ITS MODIFICATION OF CHLORPROMAZINE TOXICITY IN MICE

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1 Adult male mice were treated with caesium chloride (1.0 mEq/kg, i.p.) once daily for 54 consecutive days before administration of a single dose of reserpine (2.0 mg/kg) or (+)-amphetamine (1.0 mg/kg). Pretreatment with caesium chloride resulted in potentiation of amphetamine-produced enhancement of motility and in antagonism of reserpine-induced behavioural depression in mice as measured by a locomotor activity test, compared to the respective controls.

2 Chronic administration of caesium chloride (1.0 mEq/kg daily) with gradual dose build-up of chlorpromazine (up to 50 mg kg^{-1} day^{-1}) counteracted chlorpromazine-produced mortality in mice.

3 The results suggest an antidepressant property for Cs^+ and the combined treatment of caesium chloride with chlorpromazine might have a clinical application, i.e. in the management of chlorpromazine-induced adverse reactions.

Introduction

One rational approach for the evaluation of new drugs is to establish a relationship between changes in molecular structure and the resulting alterations in biological activity in animal experiments. Likewise, new insights into the therapeutic value of certain inorganic compounds may be obtained by an investigation of the relationship between atomic weight, physicochemical properties, and their evoked responses. For example, the demonstration of the therapeutic values of lithium (Li) salts in the management of manic states and recurrent hypomania in the manic depressive psychoses (Cade, 1949) prompted a clinical trial of rubidium (Rb) salts in the depressive illness (Fieve, Meltzer, Dunner, Levitt, Mendelewicz & Thomas, 1973), suggesting an inverse relationship between Li^+ and Rb^+ with their elicited behaviour responses. The ability of caesium (Cs) salt, another alkali metal salt, to antagonize reserpine-induced behavioural depression in mice and to potentiate the (+)-amphetamine-mediated enhancement of motility were used as experimental animal models to evaluate Cs^+ as an antidepressant. The effect of Cs^+ on chlorpromazine toxicity was also studied.

Methods

Adult male Sprague-Dawley mice weighing 20 to 27 g, were 44 days old at the beginning of the experiments and were caged in groups of three for at least two weeks before experiments were started. The animals were maintained on purina pellet chow and water *ad libitum* in an ambient room temperature of 22–25°C in a laboratory with 12 h dark/light cycles. All drugs were dissolved in 0.9% w/v NaCl solution (saline) and injected intraperitoneally in a volume not greater than 1/100 of the animal's body weight. Body weights were determined every 48 h and drug-doses were adjusted accordingly throughout the experiments. The spontaneous locomotor activity was measured by means of a selective varimax activity meter device in the vertical mode of operation (Columbus Instruments, Ohio). This allowed the vertical movements to be separated from horizontal motion while the mice were maintained in their home cages under normal light conditions.

In the first set of experiments, groups of mice, 3 mice each, were given saline or CsCl 1.0 mEq/kg, intraperitoneally, once daily for 54 consecutive days. Subsequently, saline, reserpine 2.0 mg/kg or (+)-amphetamine sulphate, 1.0 mg/kg were injected 24 h after discontinuation of pretreatment with saline or CsCl for a 54 day period. The animals' motility was then assessed over a 90 min period in response to reserpine in groups of 3 mice and to amphetamine, in mice tested alone in view of the effects of experimental

group size on amphetamine toxicity and activity (Garadocki, Schuler & Goldstein, 1966; George & Wolf, 1966). All experiments on motility were performed at the same time of day, approximately 2 h from the beginning of the light cycle, to minimize the known effects of circadian rhythm on the amphetamine-mediated responses (Scheving, Vedral & Pauly, 1968). Separate groups of Cs-treated animals were killed by decapitation for measurement of whole blood and brain content of Cs^+. Blood samples of measured volume were collected over anticoagulant and deproteinized with trichloroacetic acid (TCA). The brains were removed, weighed, rinsed with sodium phosphate buffer and homogenized with a glass homogenizer. Both blood and brain specimens were centrifuged for 30 min at 5,000 *g* and the resulting pellets were recentrifuged after washing once by resuspension in TCA and $HCLO_4$, respectively. The combined supernatants were measured for their volume and for their content of Cs^+ by atomic absorption spectroscopy. The results are expressed as mEq/l and as mEq/kg wet tissue for whole blood and brain specimens, respectively.

In a second set of experiments, which were performed at the same time as the preceding experiments, two groups of mice were administered either chlorpromazine (CPZ) alone or a mixture of CPZ and CsCl. Daily CPZ doses were maintained at 3.0 mg/kg, intraperitoneally, for both groups for an initial seven day period. This was followed by a gradual increase of CPZ dose to 50 mg/kg over a four week period (see Figure 1). The final dose of CPZ, 50 mg/kg, was maintained for a subsequent 12 days before abrupt discontinuation. CsCl was maintained at a daily 1.0 mEq/kg dose throughout the drug-treatment period. The animals' motility was measured after the initial drug treatment and once weekly during and after discontinued drug administration by means of selective varimax activity meter device as mentioned above. A mortality score (due to CNS depression as a consequence of increased dose build-up of CPZ) was recorded and expressed as % of death in mice, during a given dose regimen of CPZ, from the initial number of animals at the beginning of CPZ treatment.

The significance of the results was evaluated by the two tailed Student's *t* test for independent means.

Results

Figure 1 shows the effect of daily injection of CsCl, 1.0 mEq/kg, intraperitoneally, for 54 consecutive days on amphetamine (a) and on resperine (b) induced alteration of spontaneous locomotor activity in mice. The motility scores are given as cumulative counts and plotted as a function of time. Figure 1a illustrates the effects of prolonged pretreatment with CsCl on

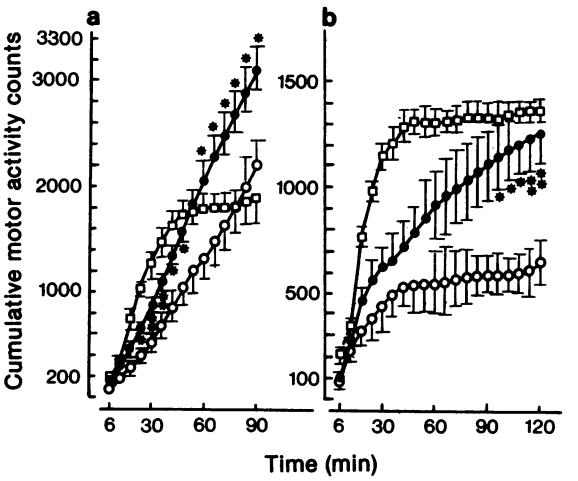

Figure 1 The effect of pretreatment with CsCl, 1.0 mEq/kg daily for 54 consecutive days on (+)-amphetamine-induced enhancement (a) and reserpine-induced depression (b) of locomotor activity in mice. (a): (●) CsCl plus amphetamine; (○) amphetamine alone; (□) CsCl alone. (b): (□) saline; (●) CsCl plus reserpine; (○) reserpine alone. Each point represents mean ± s.d. for at least 6 independent trials. $^{**}P < 0.02$; $^{*}P < 0.05$.

amphetamine-evoked enhancement of motility compared to drug-controls. Chronic administration of CsCl before a single dose of amphetamine, 1.0 mg/kg, intraperitoneally, resulted in 1.7 ($P < 0.02$) and 1.5 ($P < 0.05$) fold increase in motor activity counts for amphetamine-treated mice for the 30 min and 60 min time periods, respectively. The potentiation of amphetamine-induced effects on motility by CsCl persisted throughout the remaining 90 min ($P < 0.05$) period of measurement. Figure 1b, illustrates the effects of CsCl administration 1.0 mEq/kg daily for 54 days on reserpine-mediated behavioural depression in mice, as measured by the motility test. Cs-treated mice produced approximately two fold greater mean cumulative motor activity counts for the 102 min ($P < 0.05$) and 120 min ($P < 0.02$) periods compared to the corresponding values obtained for reserpine-treated mice. Cs-treated mice showed a 2.6 fold increase in motility from saline-treated controls for the 90 min ($P < 0.01$) trial period. Daily injection of CsCl for 54 days resulted in whole blood Cs^+ of 2.7 ± 0.3 mEq/l and whole brain Cs^+ concentration of 1.0 ± 0.2 mEq/kg wet tissue obtained 24 h after the last dose of CsCl.

Figure 2 is a graphic analysis of the experiments on the effects of chronic administration of CsCl on CPZ-produced toxicity in mice. CPZ-treated mice showed a mortality score as high as 41.7% during

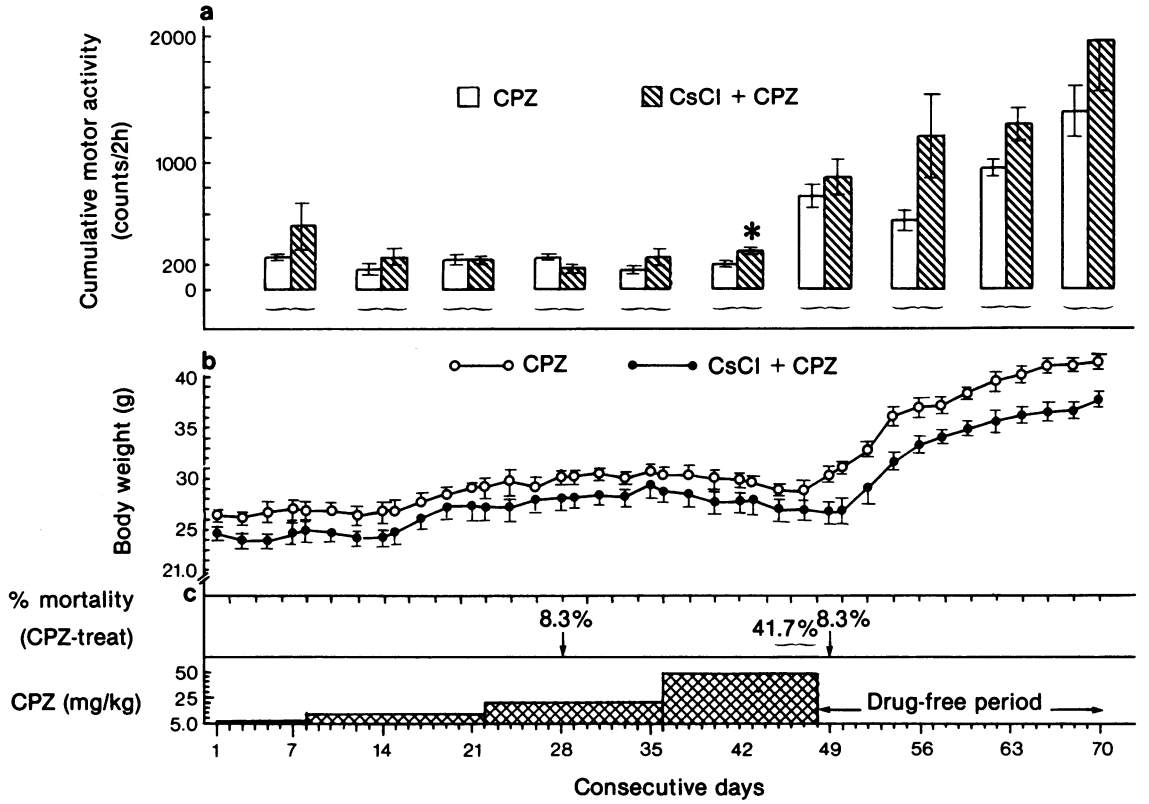

Figure 2 The effect of pretreatment of CsCl, 1.0 mEq/kg daily on chlorpromazine (CPZ) mortality in mice. (a) Gives the weekly motor activity counts for the CPZ and the CPZ plus CsCl-treated mice. In (b) the growth curve of the two groups is shown. (c) Shows CPZ dose regimens given in mg/kg of body weight followed by % mortality of mice receiving CPZ alone, with the arrows indicating period of death. The data for body weight and motor activity determinations derive from the mean ± s.e. of 5 independent determinations for 15 mice, in groups of 3, for each drug(s) treatment. $^{*}P < 0.1$.

the 50 mg kg^{-1} day^{-1} dose and a subsequent 8.3% death rate 24 h after drug-withdrawal (Figure 2c). Conversely, animals receiving the CPZ and CsCl combination all survived and tolerated the duration and the massive CPZ doses given. Furthermore, the growth rate of the two groups did not differ markedly during drug administration. A similar pattern of rebound in body weight growth was noted for both groups when drug treatment had been discontinued (Figure 2b). Figure 2a shows the cumulative motor activity counts for a 1 h period obtained immediately after drug injection on a weekly basis. In gneral, motility counts were not very different in both groups for the initial 5 weeks. This was followed by a small, but insignificant increase in motility in mice receiving the CPZ and CsCl combination compared with CPZ-treated mice which persisted during the withdrawal period.

Discussion

In the present study, using different indices of CNS excitation and depression the results show that daily administration of CsCl over a prolonged period of time enhanced amphetamine-induced hyperactivity and reduced the locomotor effects of reserpine which may be indicative of an antidepressant property of Cs^{+}. Furthermore, the Cs-evoked increase in spontaneous locomotor activity noted in this study is consistent with previous findings obtained under different experimental conditions (Messiha & Krantz, 1973;

Messiha, 1975a, b). Stimulating profile of activity shown for Cs^+ agrees with results obtained from other behavioural performance tests (Messiha & Krantz, 1973; Messiha, 1975a, b; 1976a).

Values for whole blood and brain content of exogenously administered Cs^+ agree with pharmacokinetic studies performed on mice treated for short periods with CsCl, indicating that Cs^+ is slowly absorbed and penetrates the blood brain barrier and has greater cerebral $T\frac{1}{2}$ than the other alkali metal ions studied (Messiha, 1976b). This may account for the prolonged duration of action after administration had ceased. In the present study, attempts were made to monitor CPZ-induced side effects, by a similar method to that used in rats (Boyd, 1960), involving measurement of changes in spontaneous locomotor activity. Administration of CsCl with a daily toxic dose of CPZ counteracted CPZ-evoked decreases in motility only minimally but exerted profound and persistent protective action against CPZ-caused mortality. It is notable that another alkali metal salt, Li_2CO_3 has been reported to modify certain naturally occurring and CPZ-induced neurological dyskinetic disorders of the extrapyramidal system, i.e., Huntington's Chorea (Dalen, 1973). tardive dyskinesia (Dalen, 1973; Prange, Wilson, Morris & Hall, 1973) and the dyskinetic symptoms of Gilles de la Tourette's disease (Messiha, Erickson & Goggin, 1976). Thus, it seems possible that the combined use of CsCl with CPZ may provide a new pharmacotherapeutic approach for the management of certain neuroleptic-induced side effects. Moreover, it is likely that administration of CsCl with CPZ may result in some advantage, i.e., it may be possible to increase the therapeutic dose of CPZ without a risk of major adverse reactions.

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