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Caesium ion: antagonism to chlorpromazine- and L-dopa-produced behavioural depression in mice

The efficacy of lithium salts in the treatment of manic-depressive illness (Cade, 1949) has stimulated interest in the effects of other alkali metal ions on behaviour. An antidepressant effect of rubidium salts has been suggested (Fieve, Meltzer & others, 1973). Similarities in the pharmacological effects of rubidium and caesium (Cs) salts have prompted the pre-clinical evaluation of Cs^+ as an antidepressant (Eichelman, Thoa & Perez-Cruet, 1973; Messiha & Krantz, 1973). The present study utilized the drug-induced depression in motility produced by chlorpromazine or L-dopa in mice as an experimental model to determine whether Cs^+ might have antidepressant properties.

Male Swiss albino, Sprague-Dawley mice, 8–12 weeks old, were caged in groups of six at 23–26° and had free access to Purina lab chow and water for at least two weeks before experiments. An intraperitoneal injection of CsCl (2·5 m equiv kg^{-1} day^{-1}) was administered for 5 consecutive days followed by a 48 h drug-free period before chlorpromazine (2·0 mg kg^{-1}, i.p.) or L-dopa-methylester (500·0 mg kg^{-1}, i.p.) dissolved in saline. Control injections were of isotonic saline. Injection volumes did not exceed 0·3 ml. Food was withheld for 24 h before administration of chlorpromazine, L-dopa or the control saline injection.

Spontaneous locomotor activity was measured in groups of three mice by means of a selective activity meter device (Columbus Instruments) adapted to the home cages and recorded at 10 min intervals on a digital counter beginning 10 min after administration of chlorpromazine, L-dopa or the control injection. Control and experimental groups were tested at the same time at room temperature. The statistical significance of the results was analysed by two-tailed *t*-test for independent means.

Fig. 1 shows the effects produced by short-term pretreatment with CsCl on chlorpromazine and L-dopa-mediated decrease of spontaneous locomotor activity in mice, as a function of time. Administration of chlorpromazine or L-dopa markedly decreased spontaneous locomotor activity from saline controls. Conversely, CsCl pretreatment significantly increased motility during the 40–60 min period of testing (mid panel). In general, treatment with CsCl before chlorpromazine significantly counteracted the chlorpromazine-induced decline in mice motility during the 60 min period of testing (left panel). For example administration of chloropromazine to Cs-pretreated mice resulted in mean square root motor activity counts of $16{\cdot}3 \pm 1{\cdot}7$ greater than $9{\cdot}4 \pm 1{\cdot}2$ counts obtained for the corresponding controls ($P < 0{\cdot}01$) at 20 min of the observation period. Administration of L-dopa to Cs-pretreated mice produced 34·8 and 27·7% increased motility from controls at 30 min and 60 min, respectively (right panel). However, this increase was not statistically significant. The results show that CsCl administration both increased spontaneous locomotor activity in mice and counteracted the chlorpromazine-induced decline in mice motility, while the effect of CsCl on the L-dopa-induced decrease in mice motility was less pro-

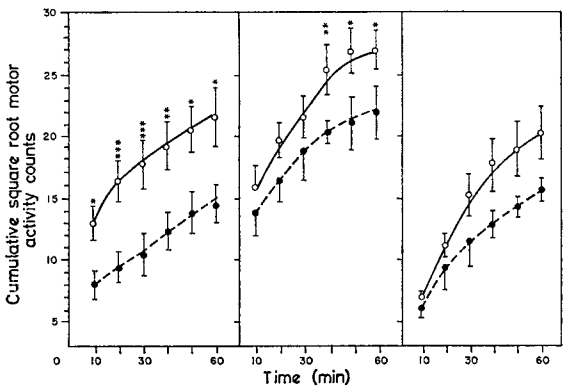

FIG. 1. The effects of CsCl pretreatment on chlorpromazine-(CPZ) and L-dopa induced decreased spontaneous locomotor activity in mice. The values are means ± s.e.m. for the cumulative activity recorded over 10 min intervals. Square root transformations were used to minimize the skewness of the distributions. Asterisks indicate the statistical significance of the difference compared to Saline pretreated levels. *** $P < 0.01$. ** $P < 0.02$. * $P < 0.05$.
Panel 1: ● Saline-CPZ, ○ Cs-CPZ. Panel 2: ● saline-saline, ○ Cs-saline. Panel 3: ● Saline-L-dopa, ○ Cs-L-dopa.

nounced. Administration of CsCl (2·5 m equiv kg^{-1} day^{-1} for 5 days) resulted in Cs^+ whole blood concentration of 0·97 ± 0·26 m equiv $litre^{-1}$ at time of testing.

Drug-produced alterations in spontaneous locomotor activity of rodents is frequently employed to test the pharmacological property of new agents. Accordingly, antagonism of reserpine-like agents, i.e. chlorpromazine-antagonism, is used for evaluation of agents with antidepressant activity (Sulser, Watts & Brodie, 1962; Sulser, Bickel & Brodie, 1964). In the present study, short-term pretreatment of mice with CsCl counteracted chlorpromazine-mediated decrease in their motor activity. This suggests that Cs^+ antagonized, at least in part, the depressant action of chlorpromazine in this experimental model. The observed increased motility of Cs-pretreated mice compared to saline-treated controls agrees with a finding obtained with smaller doses of CsCl administered orally over longer period of time (Messiha & Krantz, 1973). Thus, Cs^+ appears to possess general stimulant properties.

The foregoing observations suggest that further evaluation of Cs^+ as an antidepressant agent as well as in the management of extrapyramidal side effects (dyskinesias) produced by chronic administration of high doses of chlorpromazine or L-dopa should be undertaken.

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