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Lithium distribution in rat brain after long-term central administration by minipump

DONALD F. SMITH*, AMDI AMDISEN, *The Psychopharmacology Research Unit, Aarhus University Institute of Psychiatry, Psychiatric Hospital, DK-8240 Risskov, Denmark*

The use of lithium to treat psychic disorders has led to experiments on actions of lithium administered directly in the c.n.s. in laboratory animals. Information is available on central effects of acute lithium treatment (Mark & Watts 1971; Watts & Mark 1971; Benowitz & Sperry 1973; Inoue et al 1977; Smith 1980), but not on long-term treatments, probably because a convenient method has been lacking for prolonged central administration of lithium. Central effects of long-term lithium administration are of special interest, however, in that therapeutic actions of lithium usually appear only after several days of treatment (Schou 1968). In the present report, we describe the use of a minipump (Struyker-Boudier & Smits 1978) to administer lithium directly into the c.n.s. on a long term basis.

We used male Wistar rats (250–300 g) housed individually in a thermostatically controlled room (20 °C) on a 12-h light-dark cycle (lights on 8 a.m.). We anaesthetized eight rats with amylobarbitone and installed polyethylene cannulae (PE 60) filled with a solution of LiCl (500 mmol litre^{-1}) bilaterally in the cerebroventricles using the procedure of Biswas & Carlsson (1977). We attached a minipump (Alzet, Model 2001) containing the LiCl solution (500 mmol-litre^{-1}) to each cannula, placed the minipumps subcutaneously in the neck region, spread ampicillin in the wound, and closed the incision with sutures. In vitro studies showed the minipumps to release the LiCl solution at a constant rate (1·08 μl h^{-1}) at 37 °C.

Rats with minipumps had free access to wet-mash diet and tap water. For comparison to rats with minipumps, eight other rats were given lithium orally in the wet-mash diet containing lithium either at a dose of 40 mmol kg^{-1} dry weight for one week or 40 mmol kg^{-1} dry weight for 3 days and 60 mmol kg^{-1} dry weight for the next 4 days.

The rats were killed by an overdose of amylobarbitone after one week of lithium treatment. A blood sample was taken from the vena cava, the rats was perfused with 50 ml 0·9% NaCl (saline) administered via the left cardiac ventricle, and the brains removed. Brains and cerebral ventricles were rinsed thoroughly with saline, blotted dry and dissected into 5 parts (see Fig. 1: forebrain, hypothalamus, cerebellum, medulla oblongata and remainder). The lithium concentration in plasma and brain samples was determined spectrophotometrically using standard methods (Amdisen 1967; Smith 1976). ANOVA was used for statistical tests (Snedecor & Cochran 1967).

The distribution of lithium in brain regions and plasma after one week of lithium treatment is shown in Fig. 1. In general, the lithium distribution found resembled that seen in rats 24 h after intravenous lithium injection (Ebadi et al 1974). Statistical tests showed significant differences between the lithium concentrations in brain regions in each of the 3 groups ($P < 0.05$) with lithium concentrations significantly higher in the forebrain and hypothalamus than in the medulla oblongata and cerebellum ($P < 0.05$). Thus, the relative distribution of lithium in brain regions was similar in rats given long-term lithium treatment orally in the diet or intracerebroventricularly by minipumps. The concentration of lithium in plasma was intermediate to brain lithium levels after oral lithium intake (Treatments I and II in Fig. 1), while the plasma lithium concentration after intracerebroventricular administration by minipumps (Treatment III) was very low and lay around the limit of detection for the method used.

Daily observations on the rats indicated no marked differences in behaviour between groups, except for a moderate increase in water intake in rats given lithium in the diet compared with those given lithium by minipumps. However, supplementary studies showed intracerebroventricular administration of a LiCl solution twice as concentrated as that used in the present study to be lethal within

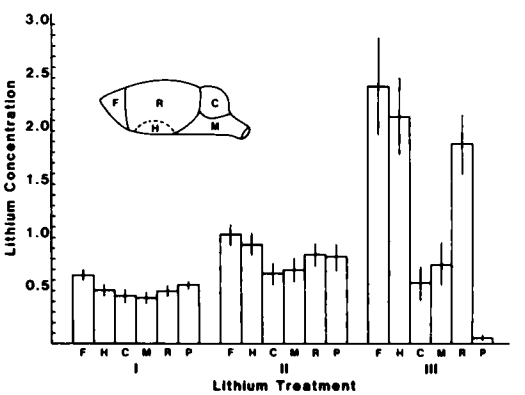

FIG. 1. Lithium concentration in brain regions (mmol kg^{-1}) and plasma (mmol litre^{-1}) in rats after 1 week of lithium treatment. Lithium was administered either orally in a diet containing 40 mmol LiCl kg^{-1} dry weight (Treatment I) or 60 mmol LiCl kg^{-1} dry weight (Treatment II) or intracerebroventricularly by bilateral injection from minipumps containing 0·5 M LiCl (Treatment III). Values shown are means ± s.e.m. for 4 or 8 rats. Abbreviations: F = forebrain, H = hypothalamus, C = cerebellum, M = medulla oblongata, R = remainder, P = plasma.

* Correspondence.

2–3 days. Nonetheless, our findings show that minipumps are suitable for administering lithium directly into the c.n.s. of rats on a long-term basis. The fact that the lithium concentration in blood is very much lower than the lithium concentration in the c.n.s. during long-term administration by minipumps suggests that the method may be of use to distinguish between peripheral and central actions of prolonged lithium treatment.

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Intrinsic activity of labetalol on guinea-pig isolated trachea

J. R. CARPENTER, *Department of Pharmacology, Materia Medica and Therapeutics, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, U.K.*

There is evidence suggesting that the combined α- and β-adrenoceptor antagonist, labetalol, has partial agonist activity on certain β-adrenoceptors systems (Whalley 1977; Nicholas et al 1978; Carey & Whalley 1979a,b; Michael 1979; Riley 1980; Whalley 1980). One example is the guinea-pig isolated trachealis muscle which relaxes in response to labetalol, the maximal effect being about 60% of that caused by full agonists, e.g. noradrenaline (Carpenter 1981).

If labetalol does possess intrinsic activity, it should be possible to produce a series of log concentration-effect curves to labetalol similar to those shown in Fig. 1 (Ariëns 1964). Each curve represents the responses to varying concentrations of partial agonist in the continuous presence of a fixed concentration of a full agonist, the curves converging at the response level corresponding to the maximum that the partial agonist can elicit on its own. Curve (i), in the absence of full agonist, is the normal log concentration-effect curve of the partial agonist.

An attempt was therefore made to generate such a set of curves from the guinea-pig isolated trachealis muscle using labetalol as the partial agonist and salbutamol as the full agonist. Guinea-pigs of either sex, from the David Lewis colony, were killed by stunning and bleeding from axillary vessels, and the trachea removed into Krebs solution. After it had been cleaned, the trachea was divided into four segments each piece being cut open longitudinally opposite the trachealis muscle, mounted on a tissue holder and attached to an isotonic transducer (Washington type T2) with a tissue loading of 1·47 mN (150 mg). The tissues were kept at 37 °C in a solution containing (mM): NaCl, 118·5; KCl, 4·8; $CaCl_2$, 2·5; KH_2PO_4, 1·4; $MgSO_4$, 1·2; $NaHCO_3$. 24·9; dextrose, 9·1, gassed with O_2 + 5% CO_2. To synchronize the development of tension and to establish the correct adjustment of the transducers, maximal relaxations were induced at the beginning of the experiment by incubating the tissues with aminophylline, 10^{-3} M, for 10 min. The tissues were then washed until a maintained contraction developed (usually 45–60 min). Occasionally, tissues failed to contract well and these were discarded so a fully

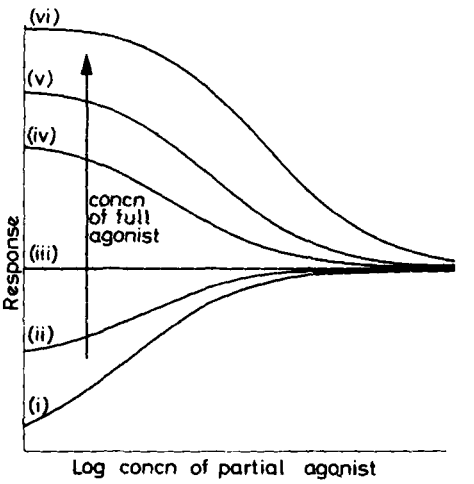

FIG. 1. Theoretical curves showing the effect of a full agonist upon responses to a partial agonist. Curve (i) is the response curve to partial agonist in the absence of full agonist. Each subsequent curve, (ii)–(vi), is the response curve to the partial agonist in the presence of different concentrations of the full agonist.