Lithium-induced head twitches in rats

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The efficacy of lithium in the treatment of mania and prophylaxis of manic depressive disorders is now accepted (Schou 1959; Schou & Braestrup 1967; Angst et al 1970). Many authors have looked for a biochemical explanation for this action and have examined the effect of lithium on the metabolism of brain catecholamines (Greenspan et al 1970; Wielosz 1974), and 5-hydroxytryptamine (5-HT) (Perez-Cruet et al 1971; Kleinrok & Wielosz 1975).

Conflicting results have been reported on the action of lithium on the metabolism of 5-HT. It has been shown that lithium treatment decreases the evoked release of 5-HT from brain slices (Katz et al 1968), stimulates uptake of 5-HT in platelets (Murphy et al 1969) or increases the rate of 5-HT synthesis (Knapp & Mandell 1973; Poitou et al 1974; Kleinrok & Wielosz 1975). It remains unclear whether the lithium-induced increase in 5-HT synthesis rate is the result of enhanced release of amine from 5-hydroxytryptaminergic neurons or of an increased intraneuronal deamination of 5-HT.

Head twitches can be used to study 5-HT neuron activity, several drugs induce these in rats, i.e. 5-hydroxytryptophan (5-HTP) by increasing the free concentration of 5-HT at its receptor site (Corne et al 1963; Nakamura & Fukushima 1976) and 5-HT or 5-methoxytryptamine by directly mimicking endogenous 5-HT at its receptors sites (Przegalinski et al 1977; Nakamura & Fukushima 1978). We report that head twitches also occur in rats treated with lithium chloride (LiCl).

The experiments were on male and female Wistar rats, 180–220 g. LiCl cyproheptadine and reserpine were dissolved in 0·9% NaCl (saline). Danitracen and methergoline were suspended in 0·5% carboxymethylcellulose solution. Danitracen, methergoline and cyproheptadine were injected intraperitoneally 1 h before LiCl, and reserpine 24 h before LiCl (150–250 mg kg^{-1} i.p.). Groups of eight rats were placed in individual plexiglas boxes (22 cm long × 10 cm high × 15 cm wide). Vehicle-injected rats served as a controls. The number of head twitches in each animal was counted every 10 min for 60 min after LiCl administration. Using 150 mg kg^{-1} LiCl as a standard response, the effect of the 5-HT antagonists (danitracen, methergoline, cyproheptadine) and reserpine which caused a decrease the concentration of brain 5-HT, and catecholamines on head twitch response was investigated.

The number of head twitches in control rats was less than 1 during 60 min observation. Spontaneous head twitches began within 15–20 min after each dose of LiCl and disappeared 60 min after injection. The number of twitches induced by LiCl increased in a dose-related manner. Maximal effect for each dose was reached at 40 min (Fig. 1). As the dose of LiCl was increased the rats became more sedated and from time to time groomed the face and cleaned the ear with a hind leg. Pretreatment with danitracen, methergoline, cyproheptadine or reserpine markedly reduced the head twitches induced by LiCl (Table 1).

Corne et al (1963) as well Nakamura & Fukushima (1978) presented evidence that 5-HTP-induced head twitches are due to a central action of 5-HT formed by decarboxylation of the amino acid. Recently Przegaliński et al (1977) described the head twitch syndrome induced by peripheral injection of 5-methoxytryptamine in pargyline-pretreated rats and suggested that it was due to direct stimulation of the central 5-HT receptors by 5-methoxytryptamine.

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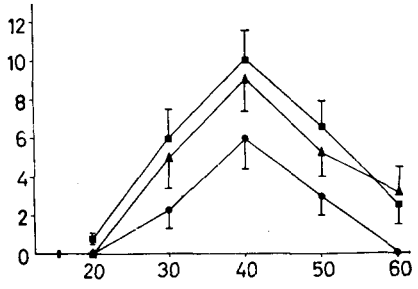

FIG. 1. Head twitches induced by several doses of LiCl, (●) 150 mg kg^{-1}, ▲ 200 mg kg^{-1}, ■ 250 mg kg^{-1}. The number of head twitches (ordinate) was counted in 10 min period for 60 min. Each point represents mean value ± s.e.m. (vertical bars) for 8 rats/group. Abscissa: time (min),

Table 1. Effect of danitracen, methergoline, cyproheptadine and reserpine on head twitches induced by LiCl. Head twitches were counted in individual rats for 60 min after administration of LiCl. Danitracen, methergoline and cyproheptadine were administered 1 h before LiCl. Reserpine was given 24 h before LiCl. Eight observations were made at each dose. Statistical significance was calculated by Student's *t*-test.

Pretreatment	Dose mg kg^{-1}	No of head twitches after treatment with LiCl 150 mg kg^{-1} (mean—s.e.m.)	*P*
Vehicle	—	21·4 ± 3·9	—
Danitracen	1	4·0 ± 1·9	<0·001
	3	2·4 ± 1·2	<0·001
Methergoline	1	5·7 ± 2·3	<0·01
	3	3·1 ± 1·0	<0·001
Cyproheptadine	0·5	11·0 ± 2·7	<0·05
	1	8·1 ± 2·6	<0·05
Reserpine	2·5	2·2 ± 0·9	<0·001

We have found that systemic administration of LiCl in high doses provokes head twitches. This effect was strongly inhibited by 5-HT receptor blockers. Thus lithium-induced head twitches could be dependent on 5-HT receptor stimulation. The question remains whether this effect represents a presynaptic or postsynaptic response. The experiments with reserpine discount the possibility that lithium-induced head twitches could be caused by the direct stimulation of 5-HT receptors. Rather they indicate they reflect a presynaptic effect on 5-HT neurons. They also suggest that during first hour of action lithium may indirectly stimulate postsynaptic 5-HT receptors in the brain and by this mechanism produce the head twitch response in rats.

In conclusion, head twitches induced by LiCl may constitute a useful animal model for quantifying 5-HT activity in the brain and screening of potential antagonists of 5-HT receptors.

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Effect of antiarrhythmic and analgesic drugs on the effective refractory period of guinea-pig isolated atria and ventricular strips

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The action of a number of antiarrhythmic agents appears to be mediated through increases in the duration of the effective refractory period (ERP) of cardiac cells (Vaughan Williams & Szekeres 1961; Baum et al 1971a,b). The refractory period varies widely in duration in various parts of the heart, being shortest in the atrial musculature and longest in the Purkinje system (Szekeres & Papp 1971). The 'following frequency' principle of Dawes (1946) has been extensively used to evaluate the effects of drugs on the ERP of isolated atria (Vaughan Williams & Szekeres 1961) and papillary muscle (Winbury 1956). However, the technique does not appear to have been widely applied to isolated ventricular strips. In this communication we have compared the effects of standard antiarrhythmic agents on the ERP of isolated atria and ventricles and also determined the actions of some strong analgesics on ERP since these drugs are widely used in cardiac patients (Lal et al 1969).

Left atria or right ventricular strips from male guinea-pigs (300–500 g) were mounted on a platinum wire electrode assembly which was suspended in oxygenated Ringer Locke solution maintained at 32 °C in a 70 ml organ bath. Square wave electrical stimuli were obtained from an SRI stimulator (8–10 V; pulse width 1 ms; frequency 2 Hz). Contractions were recorded by a force displacement transducer (Grass FTO.03) on a Mingograf 34B ink spray oscillograph (Elema Schonander). The stimulator was used to provide the driving frequency to the preparations and to trigger an oscilloscope (Tektronix 502A) sweep via a 2 position switch. Frequency was increased until the tissue could no longer follow the stimulus, as shown by the occurrence of an ectopic beat and inter-stimulus time was

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Table 1. Molar concentrations of drugs required to raise by 50% the effective refractory period (ERP) of guinea-pig isolated atrial and ventricular preparations.

Drug	Mean concentration (M) to raise ERP by 50% from control (s.e.m.) Atria	Ventricles
Propranolol	$1.52\ (0.07) \times 10^{-6}$	$1.05\ (0.31) \times 10^{-5}$
Lignocaine	$1.33\ (0.29) \times 10^{-5}$	$1.36\ (0.10) \times 10^{-5}$
Quinidine	$1.34\ (0.26) \times 10^{-5}$	$6.16\ (0.99) \times 10^{-5}$
Pentazocine	$1.41\ (0.35) \times 10^{-5}$	$1.62\ (0.16) \times 10^{-5}$
Pethidine	$1.77\ (0.28) \times 10^{-5}$	$4.02\ (0.58) \times 10^{-5}$
Procainamide	$2.39\ (0.69) \times 10^{-5}$	$7.76\ (0.62) \times 10^{-5}$
Meptazinol	$2.58\ (0.69) \times 10^{-5}$	$2.94\ (0.42) \times 10^{-5}$
Indoramin	$5.23\ (2.28) \times 10^{-6}$	$4.14\ (1.30) \times 10^{-5}$
Diphenylhydantoin	$2.09\ (0.84) \times 10^{-4}$	$1.26\ (0.36) \times 10^{-5}$
Morphine	$6.64\ (0.18) \times 10^{-4}$	$8.58\ (2.93) \times 10^{-5}$