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.

September 18, 1978

REFERENCES

Angst, J., Weis, P., Grof, P., Braestrup, P. C., Schou, M. (1970) Br. J. Psychiatry. 116: 604–614

Corne, S. J., Pickering, R. W., Warner, B. T. (1963) Br. J. Pharmacol. 20: 106–120

Greenspan, D., Aronoff, M. S., Bogdanski, D. F. (1970) Pharmacology 3: 129–136

Katz, R. J., Chase, T. N., Kopin, I. J. (1968). Science 162: 466–467

Kleinrok, Z., Wielosz, M. (1975) Pol. J. Pharmacol. Pharm. 27: Suppl. 107–112

Knapp, S., Mandell, A. J. (1973) Science 180: 645–647

Murphy, O. L., Colburn, R. W., Davis, J. M., Bunney, W. E., Jr. (1969) Life Sci. 8: 1187–1193

Nakamura, M., Fukushima, H. (1976). Psychopharmacologia. 49: 259–261

Nakamura, M., Fukushima, H. (1978) J. Pharm. Pharmacol. 30: 56–58

Perez-Cruet, J., Tagliamonte, A., Tagliamonte, P., Gessa, G. L. (1971). J. Pharmacol. Exp. Ther. 178: 325–330

Poitou, P., Guerinot, F., Bohuon, C. (1974) Psychopharmacology 38: 75–80

Przegalinski, E., Żebrowska, I., Wójcik, A., Kleinrok, Z. (1977) Pol. J. Pharmacol. Pharm. 29: 255–261

Schou, M. (1959) Psychopharmacologia. 1: 65–78

Schou, M., Braestrup, P. C. (1967). Arch. Gen. Psychiatry. 16: 162–173

Wielosz, M. (1974) Pol. J. Pharmacol. Pharm. 26: 399–409

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

S. RASHID, J. F. WATERFALL*, *Wyeth Institute of Medical Research, Huntercombe Lane South, Taplow, Maidenhead, Berks. U.K.*

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

* Correspondence.

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	$6.64\ (0.18) \times 10^{-4}$	$8.58\ (2.93) \times 10^{-5}$

determined at this point. A minimum of 3 measurements made at 2 min intervals provided control data. Readings were repeated after equilibration for 10 min with each concentration of the test drug and drug concentrations to raise the ERP by 50% of the control value were calculated. A minimum of 5 determinations were made for each drug. Molar concentrations of drugs required to raise the ERP by 50% are shown in Table 1.

Of the antiarrhythmic compounds, quinidine procainamide and propranolol (ICI) were more potent on atrial than on ventricular preparations. In support of these observations quinidine showed greater activity on isolated atria than on the papillary muscles of the cat (Dipalma & Mascatello 1951). Moreover, quinidine and procainamide significantly prolonged the atrial refractory period with minimal effects on the ventricles of the intact dog (Moe & Abildskov 1975). The finding that procainamide was less potent than quinidine on atria is in agreement with the results of Vaughan Williams & Szekeres (1961). Propranolol was the most potent of all the compounds tested on both atria and ventricles. The prolongation of ERP is probably related to its marked local anaesthetic activity (Singh & Vaughan Williams 1970). Diphenylhydantoin (Parke Davis) was approximately 16 times more potent on the ventricles than on atria. Relatively weak activity on rat and guinea-pig atria was also reported by Zetler & Strubelt (1971). Singh & Vaughan Williams (1971) have suggested that differences in action between diphenylhydantoin and the other antiarrhythmic drugs with local anaesthetic activity may be attributable to inequalities in the relative sensitivity of atrial, ventricular or Purkinje tissue.

The competitive α-adrenoceptor antagonist indoramin (Wyeth) has local anaesthetic properties and reverses arrhythmias evoked by ouabain and adrenaline (Alps et al 1971). It also increases ventricular fibrillatory threshold to electrical stimulation (Rashid & Alps 1973). In the present studies indoramin and lignocaine were equipotent on atria and ventricles; the findings for indoramin support those of Baum et al (1973) in intact dogs.

In the analgesic group of drugs, pethidine was more potent and morphine less potent on atria than ventricles. Overall, morphine was the least potent drug tested on both atria and ventricles possibly because it releases noradrenaline from sympathetic nerve terminals in the heart (Chiba 1973). Noradrenaline has been reported to lower ventricular fibrillatory threshold in isolated hearts and to increase the excitability of the myocardium (Murnaghan 1975). Pentazocine (Winthrop) and meptazinol (Wyeth) had approximately the same potencies on atrial as on ventricular preparations. Pentazocine was also the most potent analgesic drug tested with respect to its action on ERP. It possesses local anaesthetic and quinidine-like myocardial depressant properties (Fogarty et al 1970) which may explain its activity. In addition it has been reported to improve A-V nodal conduction as well as reducing automaticity (Hayakawa et al 1973). The analgesic agent meptazinol (Stephens et al 1978) is a weak local anaesthetic being approximately equipotent with pethidine in the guinea-pig skin weal test. Whilst this property may partly explain the present findings, meptazinol unlike pethidine showed moderate activity against experimental arrhythmias evoked by ouabain hypothermia and adrenaline. Since no adverse cardiovascular effects have been reported in man (Stephens et al 1978) meptazinol may be worth investigating as an analgesic in cardiac patients.

December 27, 1978

REFERENCES

Alps, B. J., Hill, M., Fidler, K., Johnson, E. S., Wilson, A. B. (1971) J. Pharm. Pharmacol. 23: 678–686

Baum, T., Eckfeld, D. K., Shropshire, A. T., Rowles, G., Varner, L. L. (1971a) Arch. Int. Pharmacodyn. Ther. 193: 149–170

Baum, T., Rowles, G., Shropshire, A. T. (1971b) J. Pharmacol. Exp. Ther. 176: 350–360

Baum, T., Shropshire, A. T., Eckfeld, D. K., Metz, N., Dinish, J. L., Peters, J. R., Butz, F., Gluckman, M. I. (1973) Arch. Int. Pharmacodyn. Ther. 204: 390–406

Chiba, S. (1973) Ibid. 206: 129–134

Dawes, G. S. (1946) Br. J. Pharmacol. Chemother. 1: 90–111

Dipalma, J. R., Mascatello, A. V. (1951) J. Pharmacol. Exp. Ther. 101: 234–248

Fogarty, M., Gill, D., Hill, P., Pettit, J. (1970). Br. J. Pharmacol. 40: 151P

Hayakawa, H., Mandel, W. J., Vyden, J. K., Parmley, W. W., Corday, E., McCullen, A., Allen, D. (1973) J. Clin. Pharmacol. 13: 313–324

Lal, S., Savidge, R. S., Chhabra, G. P. (1969) Lancet 1: 379–381

Moe, G. K., Abildskov, J. A. (1975) in: Goodman, L. S., Gilman, A. (eds) 'The pharmacological basis of therapeutics'. Collier-Macmillan, London. 5th edn, P683–704

Murnaghan, M. F. (1975) Br. J. Pharmacol. 53: 3–9

Rashid, S., Alps, B. J. (1973) J. Pharm. Pharmacol. 25: 700–704

Singh, B. N., Vaughan Williams, E. M. (1970) Br. J. Pharmacol. 38: 749–757

Singh, B. N., Vaughan Williams, E. M. (1971) Circ. Res. 29: 286–295

Stephens, R. J., Waterfall, J. F., Franklin, R. A. (1978) General Pharmacol. 9: 73–78

Szekeres, L., Papp, Gy. J. (1971). Experimental cardiac arrhythmias and antiarrhythmic drugs, Akadémiai Kiadó. Budapest. p. 17

Vaughan Williams, E. M., Szekeres, L. (1961) Br. J. Pharmacol. 17: 424–432

Winbury, M. M. (1956) Ann. N.Y. Acad. Sci. 64: 564–573

Zetler, G., Strubelt, O. (1971) Naunyn-Schmiedeberg's Arch. Pharmacol. 271: 335–345