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.

We thank Vibeke Glud and Anne-Mette Nielsen for skilful technical assistance and P. Carl Petersen's Fund and the Danish Medical Research Council for financial aid.

REFERENCES

Amdisen, A. (1967) Scand. J. Clin. Lab. Invest. 20: 104–108

Benowitz, L. I., Sperry, R. W. (1973) Exp. Neurol. 40: 540–546

Biswas, B., Carlsson, A. (1977) Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmakol. 299: 41–46

Ebadi, M. S., Simmons, V. J., Hendrickson, M. J., Lacy, P. S. (1974) Eur. J. Pharmacol. 27: 324–329

Inoue, N., Tsukada, Y., Barbeau, A. (1977) Fol. Psychiat. Neurol. Jpn. 31: 645–651

Mark, R. F., Watts, M. E. (1971) Proc. R. Soc. London. (Biol.) 178: 439–454

Schou, M. (1968) J. Psychiat. Res. 6: 67–95

Smith, D. F. (1976) Pharmacol. Biochem. Behav. 5: 379–382

Smith, D. F. (1980) Psychopharmacology 68: 315–317

Snedecor, G. W., Cochran, W. G. (1967) Statistical Methods 6th edn. Ames, Iowa: The Iowa State University Press

Struyker-Boudier, H. A. J., Smits, J. F. (1978) J. Pharm. Pharmacol. 30: 576–577

Watts, M. E., Mark, R. F. (1971) Proc. R. Soc. Lond. (Biol.) 178: 455–464

J. Pharm. Pharmacol. 1981, 33: 806–807
Communicated March 9, 1981

0022–3573/81/120806–02 $02.50/0

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

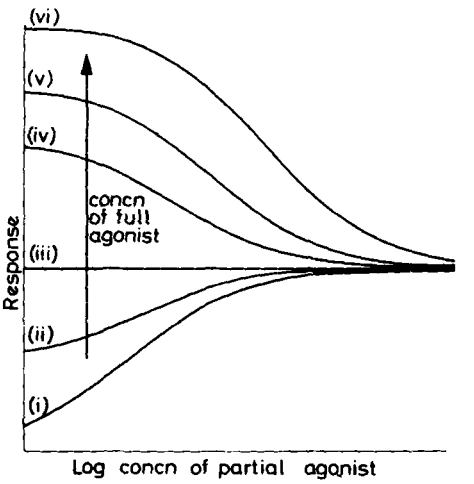

FIG. 1. Theoretical curves showing the effect of a full agonist upon responses to a partial agonist. Curve (i) is the response curve to partial agonist in the absence of full agonist. Each subsequent curve, (ii)–(vi), is the response curve to the partial agonist in the presence of different concentrations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

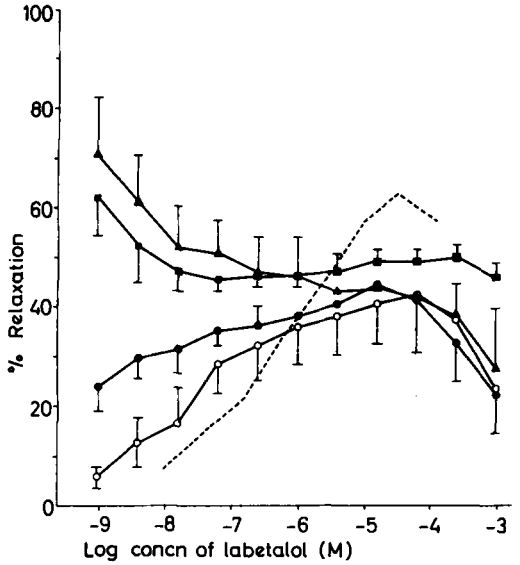

FIG. 2. The effect of salbutamol on responses of guinea-pig trachealis to labetalol. The concentrations of salbutamol were: - - - -, zero; ○, 10^{-10}; ●, 10^{-9}; ■, 10^{-8}; ▲, 10^{-7} M. Responses are means ± s.e.m. (n = 4–8) as percentages of relaxation induced by aminophylline, 10^{-3} M. (The data from the response curve in the absence of salbutamol are from another series of experiments as only four transducers were available; standard errors are ommitted for clarity.

balanced design was not possible, as on some days less than four tissues were used. Tissues were then exposed to salbutamol at concentrations of 10^{-10}, 10^{-9}, 10^{-8} or 10^{-7} M which had previously been shown to cause approximately 5, 25, 65 and 75% maximal relaxations respectively. When the response had reached a plateau, cumulative log concentration response curves to labetalol were obtained using 4-fold increments. Responses were calculated as the percentage of the maximal relaxation produced by 10^{-3} M aminophylline added after the last dose of labetalol in each cumulative curve.

The results are shown in Fig. 2. Although these curves do not match exactly those expected they clearly show some resemblance to those shown in Fig. 1. If allowance is made for the fact that the log concentration response curve to labetalol in the absence of salbutamol is bell-shaped, then the resemblance to the ideal is good. However, although such curves may be consistent with the view that labetalol is a partial agonist at tracheal β-adrenoceptors, the possibility that it acts by releasing noradrenaline is not excluded (Drew et al 1979). Foster (1963) has shown that the indirect sympathomimetic, tyramine, causes maximal relaxation of guinea-pig trachealis and the bell-shaped log concentration effect curve for labetalol on trachealis (Carpenter 1981) is what one would predict for a competitive β-adrenoceptor antagonist that also released noradrenaline.

Secondary contractions at high concentrations could arise from at least two mechanisms. Firstly, released noradrenaline would be expected to stimulate tracheal α-adrenoceptors, (which mediate contraction), as well as β-adrenoceptors. Secondly, if the maximal rate of release of noradrenaline were insufficient to cause as big a response as with exogenous noradrenaline (acting at β-adrenoceptors), concomitant competitive antagonism (at β-adrenoceptors) would be expected to progressively reduce responses if the potency of labetalol as an antagonist were less than its potency in releasing noradrenaline. However, Brittain & Levy (1976) showed that labetalol did not have a positive inotropic effect on driven guinea-pig isolated left atria and, although these authors made no other explicit statements about whether it had any stimulant effect on the hearts of anaesthetized or conscious dogs or pithed rats, it would seem reasonable to assume that they saw no such action. Also, Whalley (personal communication) could detect no stimulant effect of labetalol on rat isolated hearts. That responses to labetalol are unlikely to be due to noradrenaline release follows if it is assumed that noradrenergic nerves have similar properties whatever the tissue they innervate. Apparent intrinsic activity due to noradrenaline release would be expected to be seen in all tissues with noradrenergic innervations.

The data presented are considered to add weight to the argument that labetalol is a partial agonist at β-adrenoceptors of the guinea-pig trachea. This property may contribute to the direct peripheral vasodilation reported by Dage & Hsieh (1980), which they suggest may be partly responsible for the hypotensive properties of labetalol.

A gift of labetalol from Glaxo-Allenbury is gratefully acknowledged.

REFERENCES

Ariëns, E. J. (1964) Molecular Pharmacology, Vol. 1, Academic Press, New York and London

Brittain, R. T., Levy, G. P. (1976) Br. J. Clin. Pharmacol. Supp. 681–694

Carey, B., Whalley, E. T. (1979a) Br. J. Pharmacol. 67: 13–15

Carey, B., Whalley, E. T. (1979b) J. Pharm. Pharmacol. 31: 791–792

Carpenter, J. R. (1981) Br. J. Pharmacol. 72: 532P–533P

Dage, R. C., Hsieh, C. P. (1980) Ibid. 70: 287–293

Drew, G. M., Levy, G. P., Sullivan, A. T. (1979) Ibid. 66: 151P

Foster, R. W. (1963) Studies on the mode of action of sympathomimetic drugs with the guinea-pig isolated tracheal muscle. Ph.D. thesis, University of London

Michael, C. A. (1979) Br. J. Clin. Pharmacol. 8: 211S–215S

Nicholas, T. E., Lugg, M. A., Johnson, R. G. (1978) Proc. Aust. Physiol. Pharmacol. Soc. 9(2): 146P

Riley, A. J. (1980) Br. J. Clin. Pharmacol. 9: 517–518

Whalley, E. T. (1977) Br. J. Pharmacol. 61: 505P–506P

Whalley, E. T. (1980) Gen. Pharmacol. 11: 297–302