This investigation was supported by grants from D.G.R.S.T. and I.N.S.E.R.M.

References

AMER, M.S. (1975). Cyclic nucleotides in disease; on the biochemical etiology of hypertension. *Life Sci.*, **17**, 1021–1038.

LOWRY, D.H., ROSENBROUGH, N.J., FARR, R.L. & RANDALL, R.J. (1951). Protein measurement with the Folin reagent. *J. biol. Chem.*, **193**, 265–275.

LUGNIER, C. & STOCLET, J.C. (1974). Inhibition by papaverine of cGMP and cAMP phosphodiesterases from the rat heart. *Biochem. Pharmacol.*, **23**, 3071–3074.

THOMPSON, W.J. & APPLEMAN, M.M. (1971). Multiple cyclic phosphodiesterase activities from rat brain. *Biochemistry*, **10**, 311–316.

Evidence of central cardiovascular effects of intracerebroventricular isoprenaline in anaesthetized rat

Y. COHEN, A. LINDENBAUM, D. PORQUET & J. WEPIERRE

Laboratoire de Pharmacodynamie, Centre d'Etudes pharmaceutiques, 92290, Chatenay Malabry, France

Isoprenaline (1, 2 and 4 μg) injected intracerebroventricularly in urethane anaesthetized rat produced a long lasting hypotension and tachycardia. It is unlikely that these effects are related to leakage in peripheral circulation of the amine because: (1) After intraventricular injection, [^{3}H]-isoprenaline diffused partially out of the central nervous system, but maximal blood and heart levels measured 5 min after administration were about 2 ng/g. These concentrations were unable to induce cardiovascular effects when injected intravenously. (2) In rats cephalic cross-circulation experiments indicated that intraventricular injection of 8 μg isoprenaline to the rat donor produced tachycardia which was not observed in the second animal.

The present study showed that isoprenaline had mainly central cardiovascular effects after intracerebroventricular injection.

Characteristics and altered sensitivity of cerebral β-adrenoceptors assessed by [^{3}H]-propranolol binding

S.R. NAHORSKI & BRENDA M. SMITH

Department of Pharmacology and Therapeutics, School of Medicine, University of Leicester, Leicester, LE1 7RH, and Department of Pharmacology, University of Sheffield, Sheffield, S10 2TN

Studies on the nature and characteristics of the β-adrenoceptor have been greatly assisted by the observation that in many tissues this receptor is closely associated with the enzyme adenylate cyclase (Robison, Butcher & Sutherland, 1971). We have previously utilized this approach in assessing catecholamine-induced cyclic AMP formation in chick cerebral hemispheres and have provided evidence that these effects are mediated by a βadrenoceptor (Nahorski, Rogers, Smith & Anson, 1975). In the present study we have extended our experiments on the characterization of this receptor by examining the binding of ^{3}H propranolol, a specific ligand for the β-adrenoceptor (Nahorski, 1976), to chick cerebral membranes.

Experiments were performed on 1–6 day old male Ranger chicks. Cyclic AMP formation was determined in 0.37 mm incubated slices of the cerebral hemispheres by a protein binding assay. [^{3}H] (±)-propranolol binding was examined in a crude synaptic membrane fraction prepared by differential centrifugation (Nahorski, 1976). The order of potency of the catecholamines to stimulate cyclic AMP formation, isoprenaline > adrenaline > noradrenaline, was also observed in the ability of these compounds to displace [^{3}H]-propranolol from membrane binding sites. Salbutamol, although only a partial agonist, had a similar potency to adrenaline in both of these systems and dopamine was inactive at concentrations up to 100 μM.

(–)-Propranolol was a potent antagonist of isoprenaline (1 μM)-stimulated cyclic AMP formation ($IC_{50} = 7 \times 10^{-8}$ M) and [^{3}H]-propranolol binding ($IC_{50} = 1 \times 10^{-8}$M). (+)-Propranolol was about 100-fold less potent in both systems. H35/25(1-(*p*-tolyl)-2-isopropylamino-1-propanol), a relatively specific β_2-

adrenoceptor antagonist (Carlsson, Ablat, Brandström & Carlsson, 1972), was about 300–500-fold more potent than the cardioselective β_1-adrenoceptor antagonists, metoprolol and practolol in its ability to antagonize isoprenaline-stimulated cyclic AMP formation and [^{3}H]-propranolol binding.

In previous experiments we have demonstrated that chronic depletion of cerebral catecholamines results in an increased responsiveness of β-adrenoceptor mediated cyclic AMP formation whereas chronic isoprenaline administration induces a loss of sensitivity of this response (Nahorski & Rogers, 1975). In order to assess the possibility of an altered affinity and/or number of cerebral receptor sites in these conditions, the binding of [^{3}H]-propranolol was examined in cerebral membranes of these animals. The affinity and total number of [^{3}H]-propranolol binding sites were identical in reserpine (3 x 2.5 mg/kg) and vehicle-treated chicks. However, following isoprenaline treatment (2 x 150 μmol/kg) the loss of β-adrenoceptor responsiveness was accompanied by a significant (25–30%) apparent loss of total binding sites.

The experiments described suggest that the β-adrenoceptor in chick cerebral hemispheres resembles that found in bronchial and vascular smooth muscle (β_2) rather than that in heart (β_1). In addition evidence is presented to suggest that the loss of responsiveness of cerebral β-adrenoceptors following chronic exposure to isoprenaline is associated with a loss of available receptor binding sites.

References

CARLSSON, E., ABLAT, B., BRANDSTRÖM, A. & CARLSSON, B. (1972). Differentiated blockade of chronotropic effects of different adrenergic stimulants in cat heart. *Life Sci.*, **11**, 953–958.

NAHORSKI, S.R. (1976). Association of high affinity stereospecific binding of ^{3}H-propranolol to cerebral membranes with β-adrenoceptors. *Nature (Lond.)*, **259**, 488–489.

NAHORSKI, S.R. & ROGERS, K.J. (1975). Altered sensitivity of β-adrenoceptor-mediated cyclic AMP formation in brain. *Br. J. Pharmac.*, **55**, 300–301P.

NAHORSKI, S.R., ROGERS, K.J., SMITH, B.M. & ANSON, J. (1975). Characterisation of the adrenoceptor mediating changes in cyclic adenosine 3′-5′-monophosphate in chick cerebral hemispheres. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **291**, 101–110.

ROBISON, G.A., BUTCHER, R.W. & SUTHERLAND, E.W. (1971). Cyclic AMP. New York: Academic Press.

Peripheral effects of the amphetamine-type anorectic drugs: inhibition of catecholamine-induced lipolysis, respiration, glucose utilization in the adipose tissue of man and rat

M. DUBOST, A. ESCOUSSE, J. MOUNIÉ & R. TRUCHOT

Laboratory of Medical Pharmacology, University of Dijon

Some phenylethylamine derivatives are among the most important anorectic drugs which act by a central mechanism, but their peripheral metabolic actions are poorly understood.

It appears that many of the amphetamine drugs are weak agonists of the lipolysis in adipose cells but an inhibitory effect of sympathomimetically-induced lipolysis was found in the case of fenfluramine. The main body of work reported in this field has been carried out in the rat, the adipose adrenoceptor of which may well be quite different from that in man.

For this reason it seemed essential to investigate the effects of amphetamine anorectic drugs in both species (rat and man) on: (a) The adrenoceptor agonist activity for lipolysis, respiration, glucose oxidation of the

Table 1

Products	*Species*	*Lipolysis with theophylline*	*Lipolysis with theophylline + NA*	*Respiration*
Fenfluramine	Man	↓	↓	↑
	Rat	no effect	↓	no effect
Fenproporex	Man	↓	↓	↓
	Rat	↓	↓	↓
Chlorphentermine	Man	no effect	↓	↓
	Rat	↓	↓	↓