Effect of adrenergic substances on oxygen consumption of rat brain tissue

The influence of adrenaline and similarly acting substances on the oxygen consumption of brain tissue remains ill-understood. We have assessed the effects of noradrenaline, adrenaline and isoprenaline on the oxygen consumption of rat brain, *in vitro*.

The oxygen uptake of brain cortical slices was measured by a conventional manometric technique in an atmosphere of pure oxygen, at 37° (Umbreit, Burris & Stuffer, 1957). Krebs-Ringer phosphate solution (pH 7·4) with glucose (13 mM) was used as a buffer.

Freshly prepared solutions of noradrenaline, adrenaline and isoprenaline at final concentrations of 10^{-5}M were added to the incubation buffer at the beginning of experiments. Propranolol and dibenzyline (final concentrations 10^{-5}M) were also used in the same manner or were added to the incubation medium immediately before the amines.

The results are expressed in the μM of oxygen consumed per mg fresh tissue per hour.

Adrenaline and isoprenaline stimulate the oxygen consumption of brain cortical slices (Table 1). The strongest stimulation (about 67%) was obtained in the presence of isoprenaline while the figure was about 38% for adrenaline. The difference is statistically significant ($P < 0.001$). On the contrary, noradrenaline, 10^{-5}M did not change the oxygen uptake of cortical tissue.

Table 1. *Effect of adrenergic stimulants and antagonists on the oxygen consumption of rat brain cortical slices*, in vitro.

Substances (10^{-5}M)	QO_2 (μM O_2 mg^{-1} h^{-1})	Change of normal (%)
—	74·2 ± 1·328 (20)	—
Adrenaline	102·8 ± 2·4* (12)	+38·5
Isoprenaline	124·1 ± 6·3* (12)	+ 67·2
Noradrenaline	73·0 ± 5·8 (12)	− 1·6
Adrenaline + dibenzyline	102·0 ± 3·1* (12)	+37·6
Isoprenaline + propranolol	65·2 ± 2·7 (12)	−12·1
Dibenzyline	85·8 ± 4·1 (12)	+15·6
Propranolol	65·2 ± 4·0 (12)	− 8·1

* Mean values differ significantly ($P < 0.001$) as determined by *t*-test. Values in parentheses represent the number of experiments.

Propranolol and dibenzyline, 10^{-5}M, do not influence the oxygen consumption of brain tissue. However, the same concentration of propranolol added to the incubation buffer immediately before isoprenaline abolished the isoprenaline-stimulation of oxygen consumption. Dibenzyline did not influence the adrenaline like stimulation of the respiratory activity of rat brain tissue.

Results show that adrenaline and isoprenaline, substances acting on β-adrenoceptors, stimulated the cellular respiration of cortical slices, whereas noradrenaline did not. Propranolol, which in small doses does not change oxygen consumption of rats (Egle, Meredith & Little, 1967), completely abolished stimulation of oxygen consumption caused by adrenaline and isoprenaline.

These findings indicate that the stimulation of oxygen uptake of rat brain cortical tissue by isoprenaline and adrenaline is, probably, the response of stimulation of β-adrenoceptors.

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Effects of phenoxybenzamine, aceperone and clonidine on the level of 3-methoxy-4-hydroxyphenylglycol (MOPEG) in rat brain

In the central nervous system, α-adrenoceptor antagonists have been shown to increase noradrenaline turnover, measured either by the increase in [^{14}C]noradrenaline synthesis after intravenous [^{14}C]tyrosine (Dairman, Gordon & others, 1968) or by the disappearance of endogenous noradrenaline after synthesis inhibition (Corrodi, Fuxe & Hökfelt, 1967; Andén, Corrodi & Fuxe, 1972). On the contrary, the α-adrenoceptor agonist, clonidine (Andén, Corrodi & others, 1970), has been shown to decrease central noradrenaline turnover (Andén & others, 1970). In *in vitro* tissue preparations α-adrenoceptor antagonists and agonists have been shown to increase and decrease stimulation-induced noradrenaline overflow respectively, and these results have been interpreted in terms of compensatory changes in noradrenaline release following decreased or increased α-adrenoceptor activity (Farnebo & Hamberger, 1971; Starke & Altmann, 1973; Häggendal, Johansson & others, 1972; Potter, Chubb & others, 1971; Enero, Langer & others, 1972).

To achieve some information about whether the changes in noradrenaline turnover in the central nervous system *in vivo* following α-adrenoceptor active drugs are in any way related to changes in central noradrenaline release, I have studied the effect of the α-adrenoceptor antagonists, aceperone (Janssen, Niemegeers & others, 1967) and phenoxybenzamine, and the α-adrenoceptor agonist, clonidine, on the level of 3-methoxy-4-hydroxyphenylglycol (MOPEG) in the cns of rats. The endogenous level of MOPEG in the cns has not previously been used as a measure of central noradrenaline release, but recent experiments indicate that the level of MOPEG is useful for this purpose (Braestrup, Nielsen & others, in preparation; Walter & Eccleston, 1972, 1973; Korf, Aghajanian & Roth, 1973). The consistent results obtained in the present study further validate the use of this new technique.

Male Wistar rats, about 270 g, kept at room temperature (22°), were injected with one of the following drugs: aceperone (20 mg kg^{-1}), phenoxybenzamine (20 mg kg^{-1}), clonidine (0·5 mg kg^{-1}), protriptyline (10 mg kg^{-1}) or saline (1 ml kg^{-1}). One to 4 h after drug administration, animals were decapitated and total MOPEG, or in some experiments free MOPEG, was estimated in saline controls in parallel with drug-treated animals as described previously (Braestrup, 1973). Brains were homogenized in acetic acid, conjugates were hydrolysed with glusulase, MOPEG was extracted into ethyl acetate and the pentafluoropropionyl derivative was prepared for g.l.c. on an OV-17 column followed by electron capture detection. Analyses of variance followed by *t*-tests of control versus drug-treated animals were used for statistical evaluation. Most values are expressed as per cent of the control with a s.e. value denoting the dispersion of the drug-treated animals only.

Phenoxybenzamine (20 mg kg^{-1}) and aceperone (20 mg kg^{-1}) both caused a signifi-