The effects of some derivatives of noradrenaline and 2-amino-1-*p*-hydroxyphenylethanol on the *in vitro* mobilisation of fat

SIR,—The structure-activity relations of sympathomimetic amines show mobilisation of fat to be associated with primary or secondary amines with a hydroxyl group on the α-carbon atom of the side-chain, and on the *para*-position of the ring (Mueller & Horwitz, 1962); alkyl substitution on the β-carbon atom of the side-chain is without marked influence on the fat mobilising action (Rudman, Garcia, Brown, Malkin & Perl, 1964). The importance of the substitution on the amino-group of catecholamines has hitherto been established only in experiments using the monoethyl and isopropyl derivatives (Mühlbachova, Wenke & Hynie, 1961a; Mueller & Horwitz, 1962; Rudman & others, 1964; Wenke, Mühlbachová, Schusterová, Elisová & Hynie, 1964). In the 2-amino-1-*p*-hydroxyphenylethanol series, only the action of 1-*p*-hydroxyphenyl-2-methylaminoethanol (oxedrine) has been studied (Mühlbachová & others, 1961b; Mueller & Horwitz, 1962).

We have now examined the effect on fat mobilisation of substitution in the amino-group in an homologous series of catechol and 2-amino-1-*p*-hydroxyphenylethanol derivatives. Epididymal adipose tissue of white rats of the Konarovice strain was incubated for 90 min at 37° in Krebs-Ringer phosphate buffer (pH 7·4) containing 5% human albumin and different concentrations of the drugs. The degree of the mobilisation of fat was measured by following the release of free fatty acids into the medium; these were estimated by the method of Dole (1956). The *N*-substituted derivatives examined were the methyl, ethyl, propyl, butyl, isopropyl, t-butyl and phenyl-t-butyl compounds. Dose-response curves to the substituted derivatives were constructed after making repeated parallel curves to noradrenaline, the drug chosen as a standard. The pD_2 value was obtained from van Rossum's tables (van Rossum, 1963). Relative values in relation to the corresponding noradrenaline standard ($\Delta pD_2 = pD_2x - pD_2$noradrenaline) were derived.

When the relative affinities of the series of catecholamines to mobilise fat are examined, remarkably little change within the series is found. Fig. 1 shows only a slight trend for the affinity to increase with increase in substituent size. Non-logarithmically expressed, the affinity differences between the derivatives with the smallest and those with the largest substituent groups is as little as three-fold. A fat mobilising affinity higher than that of noradrenaline was found only in isoprenaline ($P < 0{\cdot}001$), the *N*-t-butyl derivative of noradrenaline ($P < 0{\cdot}05$) and the *N*-phenyl-t-butyl derivative ($P < 0{\cdot}001$). Adrenaline had a lower affinity than noradrenaline.

In the 2-amino-1-*p*-hydroxyphenylethanol series, where in general the fat mobilising affinities were much lower than in the noradrenaline series, the increase in affinity is more clearly seen. The difference in affinity between the unsubstituted and the most substituted compound is about 16-fold. The decrease in affinity of the methyl derivative is striking (Fig. 1).

When the pD_2 values of the corresponding derivatives of both series were correlated, a close linear relation was obtained which could be expressed by the equation $y = 0{\cdot}42x + 0{\cdot}37$. This indicated that, in relation to the changes of the nitrogen substituent, the pD_2 values rise 2·5 times more steeply in the 2-amino-1-*p*-hydroxyphenylethanol series than in the noradrenaline series. Expressed non-logarithmically, the fat mobilising affinities of the noradrenaline series increase at only slightly more than the third root of the affinities in the corresponding 2-amino-1-*p*-hydroxyphenylethanol series. The affinity sequence —isopropyl > hydrogen > methyl—is well defined in both series.

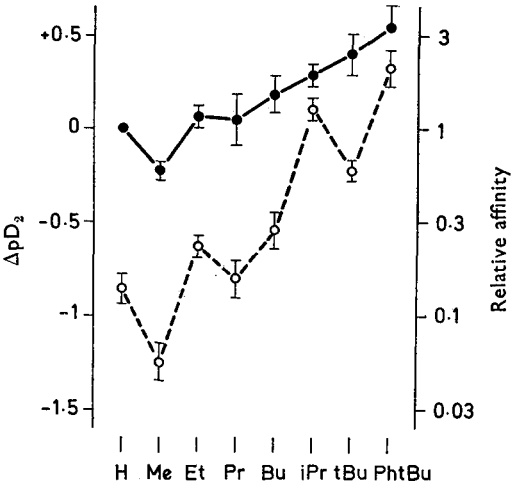

FIG. 1. ΔpD_2 values or relative affinities of both series of derivatives for their effects on fat mobilisation. Mean values ± s.e. are given. —●— Catecholamines. - - - ○ - - - 2-Amino-1-*p*-hydroxyphenylethanol derivatives.

The correlation between the slight affinity differences of the noradrenaline series and the well-graduated affinities of the parallel series, leads, therefore, to the conclusion that in the noradrenaline series there is an ascending trend of affinities towards drugs with the larger substituents, a characteristic of adrenergic reactions of the β-type.

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References

Dole, V. P. (1956). *J. clin. Invest.*, **35**, 150–154.
Mueller, P. S. & Horwitz, E. (1962). *J. Lipid Res.*, **3**, 251–255.
Mülbachová, E., Wenke, M. & Hynie, S. (1961a). *Physiologia bohemoslov.*, **10**, 181–186.
Mühlbachová, E., Wenke, M. & Hynie, S. (1961b). *Čs. fysiologie*, **10**, 355.
Rossum, J. M. van (1963). *Archs int. Pharmacodyn. Thér.*, **143**, 299–330.
Rudman, D., Garcia, L. A., Brown, S. J., Malkin, M. F. & Perl, D. (1964). *J. Lipid Res.*, **5**, 28–37.
Wenke, M., Mühlbachová, E., Schusterová, D., Elisová, K. & Hynie, S. (1964). *Int. J. Neuropharmac.*, **3**, 283–292.