EFFECT OF DRUGS BLOCKING α- AND β-ADRENERGIC RECEPTORS ON CHANGES IN LIPOLYSIS PRODUCED BY EXTRAORDINARY STIMULATION

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Extraordinary (electrical) stimulation of rats was shown to increase the concentration of non-esterified fatty acids (NEFA) in the blood serum and adipose (ependymal) tissue. All α-adrenolytics tested (sympatholytin, phenoxybenzamine, phentolamine) considerably weakened the activation of lipolysis, and reduced the increase in NEFA concentration in the adipose tissue and blood. However, against the background of isolated blocking of β-adrenergic systems by propranolol, alprenolol, and trasicor, the NEFA-mobilization reaction to extraordinary stimulation of the animals took place to the same degree as in the control rats.

Extraordinary stimulation of an animal stimulates lipolysis and increases the concentration of non-esterified fatty acids (NEFA) in the adipose tissue and blood. Some workers regard this reaction as a manifestation of a state of stress [9, 17]. The extensive literature demonstrates the important role of the sympathetic nervous system and of the catecholamines in the physiological regulation of lipolysis [13, 22, 25]. A number of investigations have been made of NEFA mobilization in response to extraordinary stimulation [1, 6, 15, 18, 21]. However, insufficient work has been done to study adrenoreceptors of adipose tissue whose excitation leads to mobilization of NEFA during extraordinary stimulation.

The first investigation was accordingly carried out in order to study the role of the sympathetic nervous system in the regulation of NEFA metabolism during extraordinary stimulation of animals by the use of adrenoreceptor blocking drugs.

Sympatholytin, phenoxybenzamine (dibenzylin) and phentolamine (regitin) were used as α-adrenoreceptor blocking drugs. As β-adrenolytics, the thoroughly investigated compound propranolol (inderal) was used, and also two comparatively new drugs blocking β-adrenergic systems, namely alprenolol ($H^{56}/_{28}$, aptin), similar to propranolol in the strength of its action [5], and also trasicor (Ciba 39,089/Ba) [24].

EXPERIMENTAL METHOD

Male rats were immobilized by attachment to a frame and then stimulated by an electric current (2.5-3 V, 50 Hz) for 2 h. The content of NEFA in the blood serum and adipose (ependymal) tissue was determined by Dole's method [11]. The compounds for testing were given in the following doses: sympatholytin 5 mg/kg, phenoxybenzamine 10 mg/kg, phentolamine 10 mg/kg, propranolol 2, 5, 10, 20, and 40 mg/kg, alprenolol 5 and 20 mg/kg, and trasicor 2, 10, and 20 mg/kg. The conditions of their administration are given in the caption to Fig. 1. Rats of the control groups received the same volumes of the corresponding solvents and were sacrificed along with the experimental animals. In a special series of experiments the effect of these compounds on NEFA metabolism was studied in intact animals kept under identical conditions with the experimental rats.

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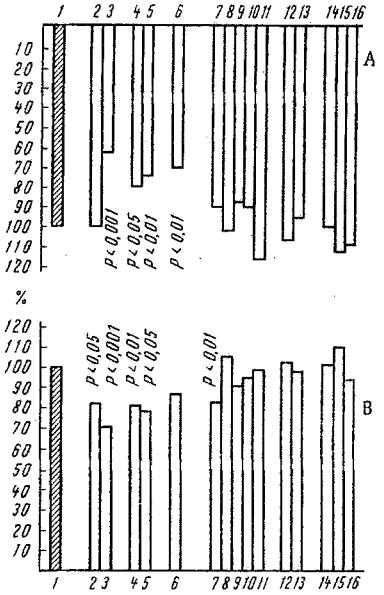

Fig. 1. Effect of adrenoreceptor blocking drugs of NEFA mobilization during extraordinary stimulation of rats: A) NEFA concentration in adipose tissue, in percent of control 2; B) NEFA concentration in blood serum, in percent of control 2; 1) control 2; 2, 3) sympatholytin 5 mg/kg, intraperitoneally 1 and 24 h respectively before stimulation; 4,5) phenoxybenzamine, 10 mg/kg, intraperitoneally 1 and 24 h before stimulation; 6) phentolamine, 10 mg/kg, intramuscularly 40 min before stimulation; 7, 8, 9, 10, 11) propranolol 2, 5, 10, 20, and 40 mg/kg respectively, intraperitoneally 30 min before stimulation; 12, 13) alprenolol 5 and 20 mg/kg respectively, intraperitoneally 30 min before stimulation; 14, 15, 16) trasicor 2, 10, and 20 mg/kg, intramuscularly 40 min before stimulation; P) significance of differences relative to control.

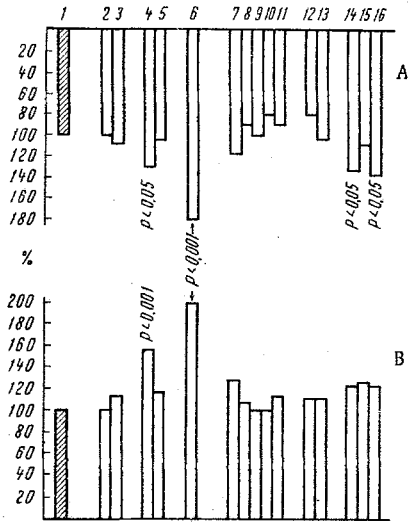

Fig. 2. Effect of adrenoreceptor blocking agents on NEFA concentration in adipose tissue and blood serum of intact animals: 1) control 1. All results expressed in percent of control 1. Remainder of legend as in Fig. 1.

The results of the experimental series were compared with those of the two control groups: 1) intact rats receiving the solvent and sacrificed along with the corresponding experimental rats; 2) animals receiving the corresponding solvent and then connected to electrical stimulation. The indices of the two control groups were taken as 100%.

EXPERIMENTAL RESULTS AND DISCUSSION

The combined action of immobilization and electrical stimulation on the animals was accompanied by an appreciable increase in the NEFA concentration in the adipose tissue and blood serum. For example, the absolute content of NEFA in the adipose tissue of rats belonging to different control groups varied from 1.9 to 2.4 μeq/g, and rose after stimulation by 1.0-1.9 μeq/g, i.e., by 50-80%. The serum NEFA level rose by 0.18-0.33 μeq/ml, or by 60-100% compared with the NEFA concentration in the control rats (control 1).

The results given in Fig. 1 show that all compounds blocking α-adrenergic systems reduced to some extent the increase in NEFA concentration in the blood serum and had a particularly marked effect in depressing their accumulation in the adipose tissue. The strongest inhibitory action on NEFA mobilization was seen when sympatholytin was injected 24 h before stimulation. The serum NEFA concentration was 29% lower, and its content in adipose tissue 37% lower than in animals exposed to extraordinary stimulation but receiving corresponding solvent instead of the compound. When sympatholytin was given 1 h before electrical stimulation, its blocking properties were weaker in their effect. Phenoxybenzamine had a similar action as sympatholytin, but differed from it in that the degree of its protective effect was practically the same whatever time it was given. Of the group of compounds blocking β-adrenoreceptors phentolamine was the least active, for it reduced the increase in NEFA only in adipose tissue. The results regarding the increase in NEFA concentration in the blood serum were not statistically significant.

The effect of the compounds blocking β-adrenoreceptors on lipolysis differed sharply from the action of those blocking α-adrenergic systems (Fig. 1). Propranolol, in a dose of 2 mg/kg, slightly reduced the increase in NEFA concentration in the blood serum but not in adipose tissue. This compound in large doses, and also alprenolol and trasicor in all doses tested, led to virtually no reduction in the increase of NEFA in either blood serum or adipose tissue during extraordinary stimulation of the rats.

Some adrenoreceptor blocking drugs themselves had a lipomobilizing effect when injected into intact rats, i.e., they increased the NEFA concentration in the adipose tissue and blood (Fig. 2). This effect was most clearly seen after administration of phentolamine: the serum NEFA concentration was doubled, and its concentration in the adipose tissue very nearly doubled. In the case of phenoxybenzamine, these lipomobilizing properties also were clearly marked, but were slightly weaker than with phentolamine. Unlike these two compounds, sympatholytin had no such effect on adipose tissue. Of the α-adrenoreceptor blocking agents, trasicor gave a very slight increase in the NEFA level, but this increase in the blood serum was not statistically significant.

Blocking the different adrenoreceptors of adipose tissue was not equally reflected in the character of the changes in NEFA metabolism produced by the combined action of immobilization and electrical stimulation of the rats. For instance, compounds blocking α-adrenoreceptors (sympatholytin, phenoxybenzamine, and phentolamine) considerably depressed the activation of lipolysis, reduced the increase in the NEFA concentration of the adipose tissue and, as a result, reduced the increase in the concentration in the blood serum. It is interesting to note that this protective action was manifested even with the use of phentolamine, which itself had a marked lipomobilizing effect, as other authors also have described [7]. However, it must be pointed out that phentolamine was weaker in its antilipemic action than sympatholytin and phenoxybenzamine. The last compound also had a lipomobilizing effect on adipose tissue, but to a lesser degree than phentolamine. According to the literature, both these blocking agents stimulate the synthesis of catecholamines and increase their blood concentration, and this was evidently one reason for their sympathomimetic effects [10].

None of the β-receptor blocking agents which were tested (propranolol, alprenolol, trasicor) prevented the increase in NEFA concentration in the adipose tissue and blood. Neither propranolol nor alprenolol reduced the stimulation of lipolysis, even when given in large doses such as 20 and 40 mg/kg, which had a marked sedative effect (some of the animals lay down on their side).

After discovering a high degree of specific antagonism between the metabolic effects of exogenous catecholamines and blocking agents, many investigators have concluded that the regulation of lipolysis in adipose tissue is effected through β-adrenergic systems [3, 12, 16, 20, 26]. However, this view is not shared by other workers [2, 4, 14, 19].

The results of the present investigation confirm the greater importance of the α-adrenergic systems of adipose tissue in the reaction of NEFA mobilization to extraordinary stimulation in rats. This agrees with the findings of Leites and Chou Su [1], who demonstrated that ergotamine effectively blocks the stimulation of lipolysis in stress (immobilization of rats).

The high inhibitory activity of α-adrenolytics with respect to NEFA mobilization in response to extraordinary stimulation, demonstrated in these experiments, could be the result of their specific antagonism with the mediator liberated at sympathetic nerve endings. On the other hand, the protective effect could be influenced by the existence of nonspecific antagonism which has been established for α-adrenoreceptor blocking agents and various lipolytic agents (such as ACTH, growth hormone, glucocorticoids, etc.) [8, 12, 16, 23].

LITERATURE CITED

1. S. M. Leites and Chou, Su, Probl. Éndokrinol., No. 5, 30 (1963).
2. R. P. Ahlquist, Ann. Rev. Pharmacol., 8, 259 (1968).
3. W. E. Barnes, J. A. Beane, R. J. Marschall, et al., Proc. Soc. Exp. Biol. (New York), 123, 643 (1966).
4. A. M. Barrett, Brit. J. Pharmacol., 25, 545 (1965).
5. P. Björntorp, L. Ek, S. Olsson, et al., Acta Pharmacol. (Copenhagen), 25, Suppl. 2, 51 (1967).
6. M. D. Bogdonoff and N. C. Durham, Arch. Intern. Med., 105, 505 (1960).
7. C. R. Boshart, L. Will, A. Pirre, et al., Fed. Proc., 20, 276 (1961).
8. W. D. Brooker and D. N. Calvert, Fed. Proc., 24, 298 (1965).

9. V. Chupkovich, G. A. Finnerty, N. Kakaviatos, et al., Circulation, 30, Suppl. 3, 61 (1964).
10. W. Dairman, R. Gordon, S. Spector, et al., Molec. Pharmacol., 4, 457 (1968).
11. V. P. Dole, J. Clin. Invest., 35, 150 (1956).
12. J. N. Fain, Ann. New York Acad. Sci., 139, 879 (1967).
13. J. Himms-Hagen, Pharmacol. Rev., 19, 367 (1967).
14. B. L. Kennedy and E. Sydney, Proc. Soc. Exp. Biol. (New York), 130, 1223 (1969).
15. A. V. Khan, R. B. Forney, and F. W. Hughes, Arch. Internat. Pharmacodyn., 151, 466 (1964).
16. J. J. Lech, Life Sci., 6, 833 (1967).
17. R. P. Maickel and R. Paoletti, Fed. Proc., 20, 276 (1961).
18. S. Malloy and P. N. Witt, J. Pharmacol. Exp. Ther., 132, 126 (1961).
19. E. Mülbachova, M. Wenke, D. Schusterova, et al., Internat. J. Neuropharmacol., 3, 217 (1964).
20. J. Nakano, T. Kusakari, and J. L. Berry, Arch. Internat. Pharmacodyn., 164, 120 (1966).
21. E. J. Printer, G. Peterfly, J. M. Cleghorn, et al., Am. J. Med. Sci., 254, 634 (1967).
22. D. Steinberg, Pharmacol. Rev., 18, 379 (1966).
23. K. Stock and E. O. Westermann, Life Sci., 5, 1667 (1966).
24. A. S. Turner and D. F. Wilson, Israel J. Med. Sci., 5, 738 (1969).
25. M. Vaugham, S. E. Berger, and D. Steinberg, J. Biol. Chem., 239, 401 (1964).
26. T. Zsoter, H. Tom, M. Kraml, et al., J. Pharmacol. Exp. Ther., 152, 425 (1966).