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Effect of Sympathetic Blocking Agent on Plasma FFA and on the Response Evoked by Catechol Amines. (28150)

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The regulatory role of the autonomic nervous system on plasma free fatty acid (FFA) has been shown in several investigations(1,2). These fatty acids with a rapid metabolic rate(3,4) are known to represent a potential pool for energy requirements(5-7) and are mobilized from fat depots, as reviewed by Bogdonoff *et al.*(8). Administration of epinephrine or norepinephrine has resulted in a prompt rise in plasma FFA concentration(9-12). The increase observed in connection with different anxiety states has also been stated to occur under the influence of these amines.

The rise in plasma FFA concentration evoked by epinephrine was counteracted by the ganglionic blocking agent hexamethonium (11), but the ganglionic blocking agent trimethaphan was without effect in this respect (13). Of the adrenergic blocking agents, which are believed to make adrenergic nerves insensitive to catechol amines, dibenzyline and dibenamine did not depress the rise in plasma FFA evoked by administered amines but ergotamine did so occasionally(13). The present experiment was carried out to observe the effect of a new type of blocking agent, the sympathetic blocking agent guanethidine*, [2-(octahydro-1'-azocinyl)-ethyl]-guanidine-sulfate, on plasma FFA concentration. This compound has a post-ganglionic blocking effect, which is believed to be mediated by the depletion of epinephrine and norepinephrine(14-15).

Materials and methods. The present experiment was carried out with 16 rabbits averaging 2.2 kg in weight (range 1950-2350 g), fed hay and standard dry-pressed food supplemented with vitamins and minerals. Food and water were allowed *ad lib.* The animals were accustomed to this diet from birth, and to the external conditions for one month before beginning the trial. The study was in 2 parts with an interval of one month. In both instances blood was taken from the ear vein at the same hour in the morning.

The first blood sample was taken just before administration of epinephrine (8 animals) or norepinephrine (8 animals). These amines were injected into the ear vein in isotonic sodium chloride solution. The dose was 2 μg/kg. After 10 minutes the second blood sample was collected from the other ear vein. The other part of the experiment was done in the same manner under the influence of the sympathetic blocking agent, which was injected into the ear vein 24 hours earlier in a dose equivalent to 15 mg guanethidine per kg. Thus each animal served as its own control. FFA was determined from the plasma(16) in duplicate, giving a reproducibility of $\pm$ 10 μEq/l. In addition blood sugar was measured by Somogyi's method.

Results. Mean values for plasma FFA and

* Ismelin®, kindly supplied by Ciba A. G., Basel.

TABLE I. Plasma Free Fatty Acid and Blood Glucose Concentrations in 16 Rabbits Before and After Administration of Sympathetic Blocking Agent, Guanethidine.

	Before admin of guanethidine	After admin of guanethidine
	Mean ± S.E.	Mean ± S.E.
Plasma free fatty acids (FFA) μEq/l	307.0 ± 29.3	183.4 ± 19.9
Blood glucose mg/100 ml	97.9 ± 2.96	99.2 ± 3.00

blood glucose concentrations in the 16 animals and corresponding figures under the influence of guanethidine are presented in Table I. The mean level of FFA (307.0 μEq/l) was lower ($P<0.02$) under the influence of guanethidine (183.4 μEq/l) than before administration of this blocking agent.

The mean rises evoked by epinephrine and norepinephrine in plasma FFA and corresponding rises evoked by these amines under the influence of guanethidine are presented in Fig. 1. The rise induced by epinephrine is somewhat lower ($P<0.05$) under the influence of this blocking agent than before its administration. On the other hand, the numerically smaller rise evoked by norepinephrine under the influence of guanethidine is not statistically significant.

Discussion. The observed decrease in plasma FFA concentration in 13 of the total series of 16 animals (average 307.0 to 183.4 μEq/l) after administration of the sympathetic blocking agent guanethidine may be a result of release of endogenous catechol amines from the tissues under the influence of this compound(14,15). In the present study guanethidine was administered 24 hours before the sample was taken, which according to Cass *et al.*(14) appears to be the time when the concentration of catechol amines in the tissues reaches a minimum after a single injection of guanethidine slightly smaller (12.5 mg/kg) than the amount used in the present experiment (15 mg/kg).

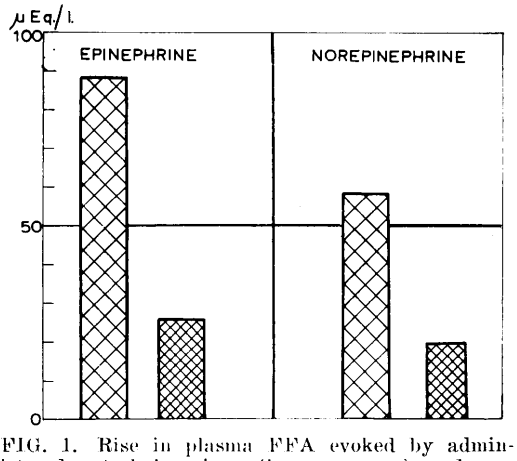

FIG. 1. Rise in plasma FFA evoked by administered catechol amines (large squares) and corresponding rise under influence of guanethidine (small squares).

As in the present findings, ganglionic blocking agents have been found to reduce plasma FFA concentration(11,17). In these experiments the compounds rapidly excreted from the organism were given in infusions and the fall in FFA level took place in some hours. On the other hand, the adrenergic blocking agents dibenamine(11), dibenzyline (13) and phentolamine(18) have been observed to raise the FFA level. This discrepancy with our results may be explained on the basis that adrenergic blocking agents may also be accompanied by release of catechol amines(19), and that at this short interval after administration of blocking agent the rise in FFA may be a manifestation of the stimulation of this release.

The rise in plasma FFA evoked by exogenous epinephrine was depressed by previously administered guanethidine. Thus under the influence of guanethidine the response to epinephrine was lowered in 7 out of 8 rabbits, but the response to norepinephrine was lowered in only 4 out of 8 animals. In previous reports the elevation of plasma FFA evoked by catechol amines was studied under the influence of adrenergic blocking agents. Havel and Goldfien(11) noticed in 2 dogs only a slight increase in plasma FFA by catechol amines under the influence of dibenamine, but McElroy and Spitzer(13) found that dibenamine and dibenzyline were without effect in this respect and ergotamine gave inconsistent results. Reports on the response of FFA to catechol amines under the influence of ganglionic blocking agents also are contradictory. The elevation in FFA evoked by exogenous catechol amines was inhibited

by hexamethonium(11) but was not reduced by trimethaphan(13).

Using threatening(17) and tilting(20) as plasma FFA elevating factors, it has been observed that ganglionic or adrenergic blocking agents counteract the rise in FFA.

The rise in blood glucose was not depressed by guanethidine. The elevation evoked by epinephrine was 28.4 mg/100 ml before administration of guanethidine, and under its influence, 25.1 mg/100 ml. Corresponding values in respect to norepinephrine were 6.4 and 1.4 mg/100 ml.

On the basis of this experiment it seems probable that the sympathetic blocking agent, guanethidine, has a depressing effect on plasma FFA level and that mobilization of FFA caused by the autonomic nervous system may also be counteracted by quanethidine.

Summary. 1) Plasma FFA concentration under the influence of a sympathetic blocking agent, guanethidine, and the effect of this blocking agent on the rise in FFA evoked by administration of epinephrine and norepinephrine in rabbits were studied. 2) Plasma FFA declined under the influence of guanethidine. 3) The rise of plasma FFA evoked by administered epinephrine was somewhat counteracted by the blocking agent. The effect of the agent on the rise evoked by norepinephrine was inconsistent.

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Studies with Mouse Pituitary Thyrotropic Tumors. VI. Monodeiodination of Tetrac. (28151)

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Mouse pituitary thyrotropic tumors *in vivo* monodeiodinate I-131 labeled L-thyroxine (T_4*) to labeled 3,5,3'triiodothyronine (T_3*)(1,2), whereas a mouse adrenotropic tumor and several other tumors and control tissues tested completely deiodinate the T_4* to iodide-131. The presence of T_3* after T_4* injection peripherally also can be demonstrated in mouse and human pituitaries(3).

The present study was undertaken to de-

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