IN VITRO EFFECTS OF TOLBUTAMIDE ON THE SYMPATHO-ADRENAL SYSTEM. Chung-Yi Hsu, Gary Brooker, Michael J. Peach, and Thomas C. Westfall, Charlottesville, Va. (Introduced by Joseph Larner,* Charlottesville, Va.)

High concentrations of tolbutamide (6.6 mM and 10 mM) provoked massive discharge of catecholamines from the perfused cat adrenal gland. Differential estimation of secreted catecholamines revealed preferential release of epinephrine by these concentrations of tolbutamide. At concentrations within the therapeutically effective range (0.1 to 1.0 mM), tolbutamide depressed basal, nicotine-, KCl-, and glucagon-induced catecholamine release from the cat adrenal glands and nicotine- and KCl-,induced ^{3}H-norepinephrine release from perfused guinea pig hearts in a dose dependent manner. This inhibitory action of tolbutamide was quickly reversed following removal of the drug from the perfusion solution. Prolonged perfusion for 20 min or longer with tolbutamide resulted in a sustained depression of catecholamine secretion from the cat adrenal. Withdrawal of the drug caused catecholamine secretion to reach a steady state level which was higher than the level observed just before tolbutamide perfusion was begun. This rebound phenomenon was occasionally manifested by an outburst of catecholamine release. Carboxytolbutamide, the major metabolite of tolbutamide, showed no effect on basal as well as stimulated catecholamine secretion. If tolbutamide acts similarly in vivo on the sympathoadrenal system, then the detailed concentration versus time relationships of tolbutamide could be of considerable importance in its pharmacological action and possible toxicological effects.

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