Inhibition of Catecholamine Release by Tolbutamide and Other Sulfonylureas

Abstract. *Tolbutamide and other sulfonylureas inhibited spontaneous and nicotine-induced release of catecholamines from the perfused cat adrenal gland and nicotine-induced release of [^{3}H]norepinephrine from isolated guinea pig hearts. Of the sulfonylureas tested, the order of potency of this inhibitory effect paralleled the hypoglycemic action. These results raise the possibility that the inhibition of the sympathoadrenal system may contribute in part to the hypoglycemic action of sulfonylureas.*

Sulfonylureas are oral hypoglycemic agents which have been utilized extensively in the treatment of adult-onset diabetes mellitus. The primary action of this group of agents has been attributed to the direct stimulation of pancreatic beta cells to release insulin (*1*). However, the poor correlation between their insulin-releasing effect and diabetic control has led to speculation of extrapancreatic actions of sulfonylureas (*2*). Herein we report an effect of tolbutamide and other sulfonylureas on the spontaneous and nicotine-induced release of catecholamines from isolated cat adrenal glands (*3*) and on nicotine-induced release of [^{3}H]norepinephrine ([^{3}H]NE) from isolated guinea pig hearts (*4*). These observations suggest that sulfonylureas have a direct inhibitory action on the sympathoadrenal system.

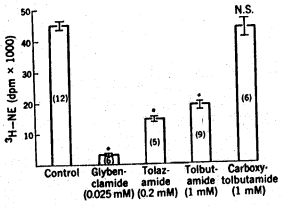

Fig. 1. The effects of four sulfonylureas on the release of [^{3}H]NE induced by nicotine in isolated guinea pig hearts, measured in disintegrations per minute. Release of [^{3}H] was stimulated by a single injection of nicotine. Five minutes before and after injection, one of the sulfonylureas or the vehicle used to dissolve sulfonylureas (control) was present. Asterisk denotes difference from control is significant at $P < .001$. *N.S.*, not significant.

Isolated cat adrenal glands were retrogradely perfused with phosphate-buffered Locke's solution, and the adrenal catecholamine secretion was monitored by a modification of the procedure of Robinson and Watts (*5*). This experimental procedure has been reported in detail previously (*6*). The effect of tolbutamide on the spontaneous secretion of catecholamines was observed by perfusing the glands with Locke's solution containing tolbutamide (0.1, 0.3, or 1 m*M*) for 5 minutes. To study the effect of sulfonylureas on the nicotine-induced release of catecholamines, each gland was stimulated twice by perfusion with nicotine ($10^{-6}M$) for 1 minute. Five minutes before and 5 minutes after the first stimulation by nicotine, the adrenal was perfused with either tolbutamide (0.3 or 1 m*M*) or tolazamide (0.2 m*M*). The administration of nicotine was repeated 30 minutes after termination of the perfusion with sulfonylureas and served as a control response.

Endogenous norepinephrine stores in isolated guinea pig hearts were prelabeled with [^{3}H]NE. Hearts were stimulated to release [^{3}H]NE by single injections of nicotine (4×10^{-7} mole) 20 minutes after [^{3}H]NE labeling. The perfusate effluents from the hearts were continuously collected and analyzed for [^{3}H]NE by liquid scintillation spectrometry (*7*). To study the effect of sulfonylureas on nicotine-induced release of myocardial [^{3}H]NE, sulfonylureas (tolbutamide, 1 m*M*; carboxytolbutamide, 1 m*M*; tolazamide, 0.2 m*M*; glybenclamide, 0.025 m*M*) were individually added to the perfusion fluid from 5 minutes before to 5 minutes after the injection of nicotine.

The spontaneous output of catecholamines from the cat adrenal gland usually became stable 1 hour after the initiation of perfusion with Locke's solution. Tolbutamide (0.3 or 1 m*M*) caused a decline in spontaneous catecholamine output (see Table 1). This inhibitory effect of tolbutamide was reversible. Nicotine-induced release of adrenal catecholamines was also suppressed by tolbutamide. When adrenal glands were stimulated consecutively at 30-minute intervals by the same dose of nicotine ($10^{-6}M$ for 1 minute), the response to the second stimulation was

Table 1. Effect of tolbutamide and tolazamide on spontaneous and nicotine-induced release of total catecholamines from isolated cat adrenal glands. Each gland served as its own control. The data are expressed as percent of control. The number of glands studied is indicated in parentheses after the mean ± S.E.M.

Drugs (m*M*)	Catecholamines released (% of control)	
	Spontaneous*	Nicotine-induced†
Tolbutamide		
0.1	95 ± 2 (3)	
0.3	72 ± 6 (5)‡	77 ± 5 (4)‡
1.0	62 ± 8 (5)‡	56 ± 10 (7)‡
Tolazamide		
0.2		51 ± 7 (3)‡

* [Rate of spontaneous output in the presence of sulfonylurea (ng/min) divided by the rate of spontaneous output in the absence of sulfonylurea (ng/min)] × 100. Control spontaneous output was 230 ± 30 ng/min. † [Nicotine-induced release in the presence of sulfonylurea (ng) divided by nicotine-induced release in the absence of sulfonylurea (ng) × 100. Control nicotine-induced release was 12,210 ± 1,330 ng. ‡ Signifiant at $P < .01$