PRELIMINARY NOTES

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The sodium pump and insulin secretion

In view of the fundamental role of transmembrane sodium flux in such excitatory phenomena as skeletal muscle contraction or nerve conduction, sodium fluxes might also be involved in the excitation of secretion. The possible role of sodium in the release of insulin from the β cell has been investigated by studying insulin secretion from rabbit pancreas *in vitro* in different ionic media and in response to ouabain, a glycoside which inhibits the sodium pump in other tissues[1].

Pieces of pancreas from 4–8-week-old rabbits were incubated *in vitro*[2] and insulin secretion into the incubation medium was measured[3] during exposure of the pancreas to stimuli in media of differing ionic compositions. Glucose, L-leucine, glucagon and tolbutamide were selected as stimuli to provide a wide range of signals for insulin secretion[4]. Krebs–Henseleit medium supplemented with sodium pyruvate, glutamate and fumarate[5] and 3.3 mM glucose was used in all experiments except those in which glucagon was the stimulus when 16.5 mM glucose was added. Sodium was replaced by choline in media from which it was omitted.

The effect of 10^{-8} to 10^{-5} M ouabain on insulin secretion was studied by ex-

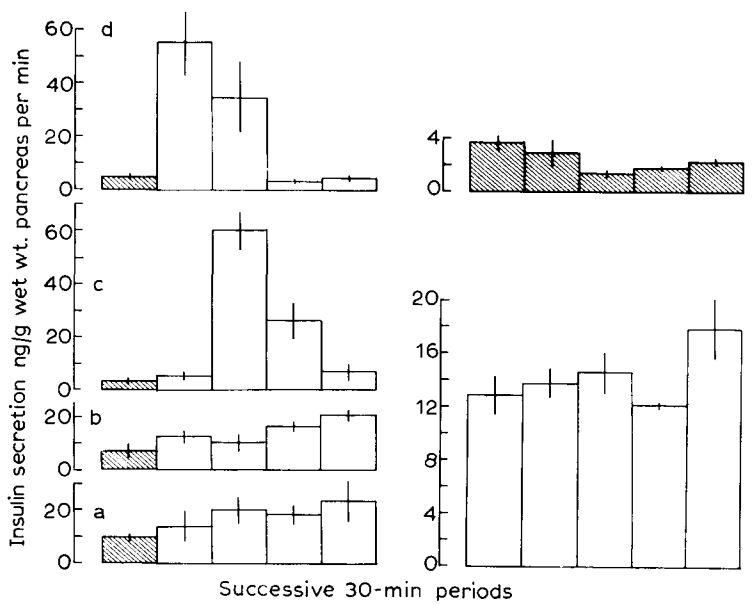

Fig. 1. Mean rate of insulin secretion (± S.E.) from rabbit pancreas *in vitro* under control conditions (shaded rectangles) and in response to ouabain (open rectangles) at concentrations of 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} M in Expts. a, b, c and d, respectively. Each value was the mean of 5 observations and each experiment was preceded by a 60-min preincubation period.

Fig. 2. Mean rate of insulin secretion (± S.E.) from rabbit pancreas *in vitro* in Krebs–Henseleit medium containing 3.3 mM glucose (shaded rectangles) compared with that in a medium in which potassium had been replaced by sodium (open rectangles). Conditions as in Fig. 1.

TABLE I

THE EFFECT OF SODIUM REPLACEMENT ON INSULIN SECRETION FROM RABBIT PANCREAS IN RESPONSE TO VARIOUS STIMULI

Each incubation period was 30 min and no measurements were made in periods 1, 4 and 7 which were to establish a steady state. In experiments marked with an asterisk the first three incubation periods were omitted.

Stimulus	*Number of observations*	*Mean insulin secretion ± S.E. (ng/min per g wet wt. pancreas)*								
		$+Na^+$			$-Na^+$			$+Na^+$		
		1	*2* Basal	*3* Stimulated	*4*	*5* Basal	*6* Stimulated	*7*	*8* Basal	*9* Stimulated
16.5 mM glucose	6		4.1 ± 0.7	28.7 ± 3.6		6.5 ± 1.4	8.0 ± 1.4		2.0 ± 0.4	11.3 ± 2.2
	6*					22.7 ± 3.2	24.8 ± 7.7		16.6 ± 3.3	49.6 ± 8.7
5 mM L-leucine	5		3.6 ± 1.2	10.1 ± 3.4		7.6 ± 1.1	10.1 ± 2.2		3.7 ± 0.5	16.3 ± 4.7
	5*					20.1 ± 6.0	16.4 ± 3.6		4.1 ± 1.2	32.2 ± 7.6
5 μg/ml glucagon	5		155.0 ± 22.5	316.0 ± 85.0		92.0 ± 10.8	60.0 ± 1.4		29.0 ± 8.9	54.0 ± 3.5
	5*					16.5 ± 3.3	11.1 ± 2.9		11.8 ± 2.9	43.3 ± 8.2
200 μg/ml tolbutamide	5		2.6 ± 0.6	10.9 ± 1.9		9.8 ± 3.5	9.1 ± 1.6		1.6 ± 0.1	5.2 ± 1.0
	5*					13.4 ± 2.1	8.9 ± 1.2		16.0 ± 2.2	25.7 ± 3.6
10^{-5} M ouabain	5*					6.7 ± 1.0	5.9 ± 3.6		12.2 ± 1.0	23.8 ± 1.4
	5*					6.1 ± 0.9	3.9 ± 0.6		7.6 ± 0.7	13.5 ± 2.3

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posing pieces of pancreas to ouabain for four 30-min periods (Fig. 1). 10^{-6} and 10^{-5} M ouabain stimulated insulin secretion. It was postulated that, if the stimulation were due to inhibition of the sodium pump, omission of potassium from the incubation medium should also inhibit the pump and thereby stimulate insulin secretion. Insulin secretion from pieces of pancreas incubated in a potassium-free medium was therefore compared with that from pieces in a normal medium (Fig. 2). The omission of potassium from the incubation medium stimulated insulin secretion.

The possible dependence on extracellular sodium of other stimuli to insulin secretion was investigated by experiments in which the stimulus was added in the presence or absence of sodium.

In addition, each experiment was repeated omitting the first three periods. The results of these experiments are shown in Table I. The omission of sodium from the incubation medium inhibited the stimulation of insulin secretion (period 6) which could be demonstrated either before (period 3) or afterwards (period 9) in the presence of sodium.

The stimulation of insulin secretion by ouabain was abolished by the omission of sodium from the incubation medium but could be elicited when the medium was reconstituted (Table I). This observation suggested that the stimulation of insulin secretion either by ouabain or in potassium-free medium was secondary to a rise in the intracellular sodium concentration.

Inhibition of such diverse stimuli as glucose, L-leucine, glucagon and tolbutamide by the omission of sodium from the incubation medium suggests that the entry of sodium into the β cell may be a fundamental event in the stimulation of insulin secretion.

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