Somatostatin: Mechanism of Action in Pancreatic Islet β-Cells

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SUMMARY

The widespread role of somatostatin (SRIF) as a mediator of function in the brain and gut has stimulated interest in its mechanism of action. We have examined the mode of action of SRIF in stimulus-secretion coupling in the pancreatic islet β-cell to determine whether SRIF antagonizes the glucose-induced decrease in K^+ permeability (P_K). The influence of SRIF on ^{86}Rb fluxes and insulin release in cultured rat islet cells, and also the electrical events recorded from cultured islets and microdissected mouse islets, was examined. In cultured islets, 100 ng/ml SRIF in the presence of 16.7 mM glucose inhibited the incidence of spike activity and evoked hyperpolarization. This effect was counteracted by 0.1 mM quinine and 20 mM tetraethylammonium (TEA), drugs that inhibit the Ca^{2+}-sensitive or voltage-sensitive increase in P_K, respectively. These agents also counteracted the inhibitory influence of SRIF on glucose-induced insulin release in cultured islets. SRIF disrupted the typical glucose-induced oscillatory pattern of electrical activity (burst activity) during continuous microelectrode recordings in mouse β-cells, resulting in a transient 5 mV hyperpolarization and a decrease in the frequency of generation of burst activity. The presence of 20 mM TEA prevented the influence of SRIF on the electrical activity. SRIF had no effect on the accumulation of ^{86}Rb into islet cells obtained in the presence of 16.7 mM glucose. However, SRIF enhanced the rate of ^{86}Rb efflux from cells exposed to glucose. SRIF-induced enhancement of ^{86}Rb efflux was antagonized by TEA or quinine. These results indicate that SRIF may activate P_K as its primary mode of action, an event that may be sufficient to reduce the accumulation of intracellular Ca^{2+} thereby disrupting glucose-induced stimulus-secretion coupling. DIABETES *30*:836–842, October 1981.

The widespread role of somatostatin (SRIF, somatotropin release inhibiting factor) as a modulator of neural activity as well as endocrine and exocrine secretion has stimulated interest in its mechanism of action. Most of the available evidence concerning the mechanism of action of SRIF indicates that its primary effect resides in disrupting the transduction of receptor information at the level of the plasma membrane.[1] SRIF inhibits the generation of cyclic AMP,[2–5] decreases the membrane permeability to Ca^{2+},[4,6,7] and disrupts the electrical activity associated with glucose-induced insulin secretion.[8] Alterations in the membrane potential and in the oscillatory nature of the spike activity induced by high glucose appear to be primarily due to changes in K^+ permeability (P_K).[9–14] The ability of SRIF to antagonize glucose activation of the electrical events in the β-cell plasma membrane may be due to a countermodulatory action of SRIF on P_K.

The present study was designed to clarify the influence of SRIF on ionic mechanisms in relation to secretory changes. Specifically, the effects of SRIF on ^{86}Rb fluxes and insulin release in cultured rat islet cells, and on the electrical events recorded from cultured islets and microdissected mouse islets, were determined.

METHODS

Animals, isolation, and culture of islets. Islets of Langerhans were isolated from fed male Sprague-Dawley rats (250–300 g) by the collagenase technique[15] in combination with a Ficoll gradient.[16] Islets were cultured from 3–4 days in RPMI-1640 with the addition of 10% fetal calf serum (heat-inactivated), 100 U/ml penicillin, and 100 μg/ml streptomycin sulfate. Cultured rat islets were used in all experiments, except for the electrical studies in which microdissected mouse islets were used for continuous electrode recordings to assess the action of SRIF on a single β-cell. The islets were isolated from fed male CBA/J mice obtained from Jackson Laboratories (Bar Harbor, Maine).

Electrophysiologic studies. Within 3–4 days of culture, the islets attached to the plastic culture dish. The culture me-

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dium was replaced by a Krebs-Ringer bicarbonate-buffered medium containing, in addition, 25 mM Hepes (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid). The medium was gassed with 95% O_2 and 5% CO_2, and maintained at 37°C. The electrophysiologic setup and procedures were as described previously.[8] Several islet cells were impaled during exposure to each medium containing the desired additions (see Table 2 for details). The membrane potential and presence of electrical activity were obtained from individual islet cells that portrayed a stable potential after at least 1 min of impalement with a microelectrode. In each experiment, 4 to 6 islet cells were successfully impaled during a 15-min period.

Microdissected mouse islets were used to ascertain the dynamic influence of SRIF on glucose-induced electrical activity recorded from a single β-cell. Briefly, islets were partially dissected from a mouse pancreas, pinned by attached blood vessels in a 0.5-ml perifusion chamber, and subjected to a flow rate of 2 ml/min. The preparation was perifused with a Krebs-Ringer bicarbonate-buffered solution maintained at 37°C, gassed with 95% O_2 and 5% CO_2, and stabilized at pH 7.4 by the addition of 25 mM Hepes. The β-cells were impaled with glass microelectrodes with tip resistances of 175–300 MΩ. The electrical events were recorded using standard electrophysiologic techniques.[17] Initial impalements were made routinely at a level of 11.1 mM glucose to identify β-cells by their characteristic pattern of electrical activity.[12,18]

^{86}Rb accumulation and efflux. Rat islets were cultured for 3–4 days, after which groups of 10–15 were placed in microcentrifuge tubes, each containing 0.2 ml of Krebs-Ringer solution with the addition of 2.8 mM glucose. After 30 min of preincubation at 37°C in an atmosphere of 95% O_2 and 5% CO_2, the tubes were centrifuged and the medium was withdrawn. A second aliquot of medium containing, in addition, 0.2 mM ^{86}RbCl (5–15 mCi/mmol) and 0.1 mM 6,6'-n^{3}H sucrose (26 mCi/mmol) was added to each tube. The islets were preloaded with the radioisotopes for 90 min for the efflux studies. The medium was subsequently removed, the islets were washed briefly, and 0.5 ml of nonradioactive medium containing the desired additions was added to each tube. The accumulation of ^{86}Rb into the islet cells was determined by adding 0.2 ml of medium containing ^{3}H-sucrose, ^{86}Rb, and the desired agents after the preincubation period. For both the accumulation and efflux studies, each tube was centrifuged at selected intervals in a Beckman microfuge (Beckman Instruments, Fullerton, California) to deposit the islets in the tip of the tube. Di-n-butyl phthalate was then layered on top of the medium, and a second centrifugation separated the medium from the islet pellet.[10] The bottom of the tube containing the islet pellet was cut off and placed in a scintillation vial. Hyamine was placed on top of the islets and the vials were incubated for 2 h at 37°C. The islets were mixed with a neutralizing cocktail and examined for their ^{86}Rb and ^{3}H content. Appropriate corrections were made for 3% spillover of ^{86}Rb counts to the ^{3}H-channel; the spillover of the ^{3}H-counts to the ^{86}Rb-channel was negligible. The ^{86}Rb remaining in the islets was corrected for the amount of ^{86}Rb residing in the extracellular space occupied by ^{3}H-sucrose. Samples of incubation media were used as external standards. Blanks without islets did not differ from the background of the counter.

Insulin release. For the secretory studies, groups of 10–15 rat islets, cultured for 3–4 days, were preincubated in an atmosphere of 95% O_2 and 5% CO_2 for 30 min at 37°C in Krebs-Ringer medium containing 0.3% (w/v) bovine serum albumin and 2.8 mM glucose. The islets were subsequently incubated in fresh medium containing the desired agents for 30 min, after which the medium was withdrawn and stored at −20°C until assayed for insulin content.[19]

Chemicals. Somatostatin was obtained from Pierce (Rockford, Illinois); tetraethylammonium chloride from Aldrich Chemical Company (Milwaukee, Wisconsin); quinine chloride and collagenase from Sigma Chemical Company (St. Louis, Missouri); ^{86}RbCl and 6,6'-n^{3}H sucrose from Amersham (Arlington Heights, Illinois); and Hepes from Calbiochem (La Jolla, California). All other chemicals were of analytic grade or the highest grade available.

Statistics. Statistical significance of data was determined by Student's *t* test, either paired or unpaired, as appropriate.

RESULTS

INSULIN RELEASE

Quinine and TEA have been used to inhibit the Ca^{2+}-dependent or voltage-dependent increase in P_K, respectively.[11,13] Both agents potentiate the secretory response to glucose in rat islets.[20,21] These agents were used in conjunction with SRIF to examine the possibility that SRIF activates the mechanism(s) controlling the increase in P_K in the β-cell membrane, thereby antagonizing the glucose-induced reduction in P_K.[22–24] Addition of 20 mM TEA reversed the inhibitory influence of 100 ng/ml SRIF on the glucose-induced secretory response of cultured islets (Table 1). The addition of 0.1 mM quinine was also an antagonist of the inhibitory influence of SRIF on glucose-induced insulin release (Table 1).

ELECTRICAL ACTIVITY

Cultured rat islets. In previously reported electrophysiologic studies, we used islets cultured in medium CMRL-1066 containing 5.6 mM glucose.[8] We subsequently found that islet cells maintained in medium containing 14 mM glucose exhibited more negative membrane potentials when examined in acute experiments.[25] In view of this we reexamined the effect of SRIF on glucose-induced electrical activity in islets cultured in RPMI-1640 containing 11 mM glucose. After 3–4 days of culture, the medium was exchanged for a buffered salt solution. The membrane potential measured in the absence of glucose was −35 ± 2 mV (M ± SE; N = 24), and in the presence of 16.7 mM glucose, it was −26 ± 2 mV (N = 19). The decrease in potential due to glucose was accompanied by an increase in the incidence of spike activity from 8 ± 2% to 56 ± 7% of the total number of cells impaled. The addition of 100 ng/ml SRIF to a medium containing 16.7 mM glucose resulted in a rapid increase in the average membrane potential (hyperpolarization) and a substantial decrease in the incidence of spike activity (Table 2). The addition of 20 mM TEA or 0.1 mM quinine almost completely antagonized the influence of SRIF on glucose-induced electrical activity (Table 2). SRIF still produced a small but significant hyperpolarization of the membrane despite the addition of TEA or quinine.

TABLE 1
Influence of quinine and TEA on the secretory response of islet cells: reversal of the inhibitory effect of somatostatin*

Experiment	TEA (20 mM)	Glucose (16.7 mM)	SRIF (100 ng/ml)	Insulin release (μU/islet/30 min)
A				
1	−	+	−	25.3 ± 4.1
2	−	+	+	8.8 ± 2.3
3	+	+	−	33.6 ± 3.1
4	+	+	+	22.0 ± 3.0
	Quinine (0.1 mM)			
B				
1	−	+	−	28.0 ± 3.7
2	−	+	+	9.7 ± 1.5
3	+	+	−	34.5 ± 4.2
4	+	+	+	19.3 ± 2.5

* Each value represents the mean ± SE of at least eight observations. The following are P values indicating the statistical significance of the secretory response in relation to a control value. NS indicates not significant.

<0.001	<0.002	<0.005	<0.02	NS
B_2 vs. B_1	A_2 vs. A_3	A_2 vs. A_1	B_4 vs. B_3	A_3 vs. A_1
			B_4 vs. B_2	A_4 vs. A_1
			A_4 vs. A_3	B_3 vs. B_1
				B_4 vs. B_1

TABLE 2
Influence of somatostatin on glucose-induced electrical activity in cultured islets: antagonistic action of TEA and quinine*

	Membrane potential (mV)			Cells exhibiting spike activity (%)		
	0–15 min	15–30 min	P value	0–15 min	15–30 min	P value
A	Glucose (−28 ± 3)	Glucose + SRIF (−52 ± 5)	<0.001	Glucose (50 ± 6)	Glucose + SRIF (18 ± 5)	<0.001
B	Glucose + TEA (−23 ± 3)	Glucose + TEA + SRIF (−30 ± 3)	NS	Glucose + TEA (60 ± 6)	Glucose + TEA + SRIF (50 ± 3)	NS
C	Glucose + quinine (−18 ± 4)	Glucose + quinine + SRIF (−25 ± 3)	NS	Glucose + quinine (62 ± 8)	Glucose + quinine + SRIF (56 ± 5)	NS

* Each value represents the mean ± SE of a total of at least 12 cells impaled in three separate experiments. The concentrations of the agents are glucose, 16.7 mM; SRIF, 100 ng/ml; TEA, 20 mM; and quinine, 0.1 mM.

TABLE 3
Influence of somatostatin on glucose-induced electrical activity

	Silent phase* (s)			Active phase* (s)			
Experiment	Glucose A	Glucose + SRIF B	B/A	Glucose A	Glucose + SRIF B	B/A	Hyperpolarization† (mV)
1	14	29	2.1	11	15	1.4	6
2	14	19	1.4	11	9	0.8	4
3	8	21	2.6	7	4	0.6	6
4	9	20	2.2	6	3	0.5	6
5	12	20	1.7	5	4	1.0	4
(mean ± SE)	11 ± 1	22 ± 2‡	2.0 ± 0.2	8 ± 1	7 ± 2§	0.9 ± 0.2	5.2 ± 0.4

* Averaged over a period of 3 min before (A) or after (B) SRIF was added to the preparation. (The electrical activity recorded during the period of chamber mixing was not quantitated for this evaluation.)
† Maximum change in membrane potential (hyperpolarization) following addition of 100 ng/ml SRIF to the medium. Each β-cell was initially impaled in 11.1 mM glucose after which 100 ng/ml SRIF was added to the medium.
‡ $P < 0.001$ for the statistical significance of B vs. A.
§ There is no statistically significant difference for B vs. A.

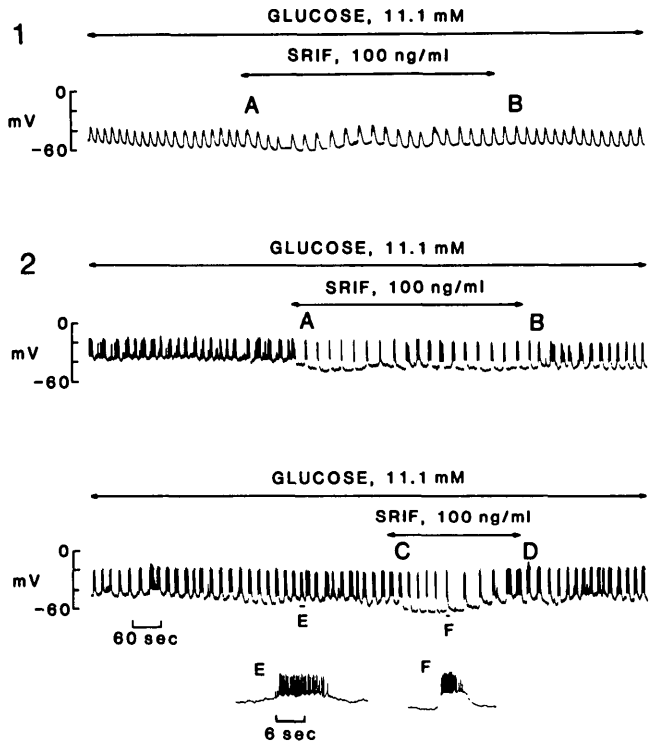


FIGURE 1. Influence of SRIF on glucose-induced electrical activity during continuous recording from individual β-cells located in a microdissected mouse islet. Glucose was present throughout the recordings obtained from cells 1 and 2. In both cells, SRIF was added to the preparation at A and withdrawn at B. In cell 2, SRIF was added for a second period at C and withdrawn at D. Record E or F shows a burst of electrical activity at fast record speed.

Microdissected mouse islets. Figure 1 shows the influence of SRIF on the electrical activity of two different β-cells. SRIF rapidly evoked a slight lengthening and increased the extent of hyperpolarization of the silent phase. The effect was transient, lasting for about 3–4 min. Following the removal of SRIF from the solution, cell 1 returned to its control activity. Cell 2 did not return to its control activity, but continued to show hyperpolarization during the silent phase, although not to the extent seen when SRIF was present. A second exposure of cell 2 to SRIF elicited a transient increase in the duration of the silent phase and hyperpolarization.

On the average, SRIF doubled the duration of the silent phase, had no effect on the duration of the active phase, and provoked a transient hyperpolarization (Table 3). After about 3 min in the presence of SRIF, the increase in both the duration of the silent phase and the membrane potential gradually returned to pre-SRIF values (data not shown). However, the overall pattern of electrical activity was often quite irregular when compared with the patterns observed either immediately before or after the addition of SRIF.

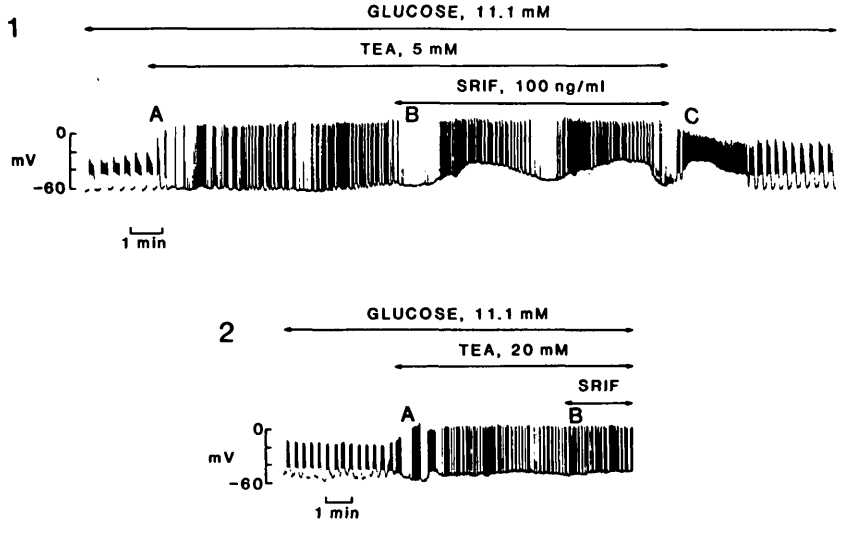
In Figure 2, 5 mM TEA is shown to abolish the oscillatory pattern of electrical activity observed in the presence of 11.1 mM glucose.[13,26] After TEA, SRIF introduction to the preparation rapidly induced a transient loss of spike activity. In the intervals between the silent phases there was depolarization accompanied by fast spikes. After the removal of both TEA and SRIF, the cell exhibited a biphasic pattern of electrical activity. SRIF (100 ng/ml) had no effect on the electrical events elicited by 20 mM TEA (Figure 2). In additional experiments with 20 mM TEA, SRIF up to 500 ng/ml had no effect on the electrical activity (data not shown).

^{86}Rb ACCUMULATION AND EFFLUX

SRIF had no apparent influence on the uptake of ^{86}Rb into islet cells over a 30-min period as compared with that obtained in the presence of 16.7 mM glucose alone (Figure 3). However, SRIF significantly enhanced the rate of ^{86}Rb efflux from cells exposed to 16.7 mM glucose (Figure 4). In agreement with the results of other investigators,[22–24] glucose decreased the rate of ^{86}Rb efflux from islet cells (Figure 4). The addition of SRIF to medium containing 5.6 mM glucose led to a 1.4-fold increase in the rate constant for ^{86}Rb efflux, whereas with 16.7 mM glucose SRIF provoked a 1.8-fold increase in the rate of ^{86}Rb efflux. The glucose-induced reduction of ^{86}Rb efflux was not further reduced by the addition of 20 mM TEA (Figure 5). However, the enhancement of the rate of ^{86}Rb efflux due to SRIF was substantially reduced by the simultaneous presence of TEA. In addition, 0.1 mM quinine partially reversed the SRIF-induced increase in the rate of ^{86}Rb efflux (Table 4).

An increase in Ca^{2+} from 2.5 to 5.0 mM or the addition of SRIF to a medium containing 16.7 mM glucose produced a similar increment in the efflux rate of ^{86}Rb when acting separately; when working together, there was an additional aug-

FIGURE 2. Influence of SRIF on electrical activity due to glucose and TEA during continuous recordings in mouse islet β-cells. Glucose was present throughout the recordings. With both cells 1 and 2 TEA was added at A and SRIF was added at B. Both TEA and SRIF were withdrawn from cell 1 at C.



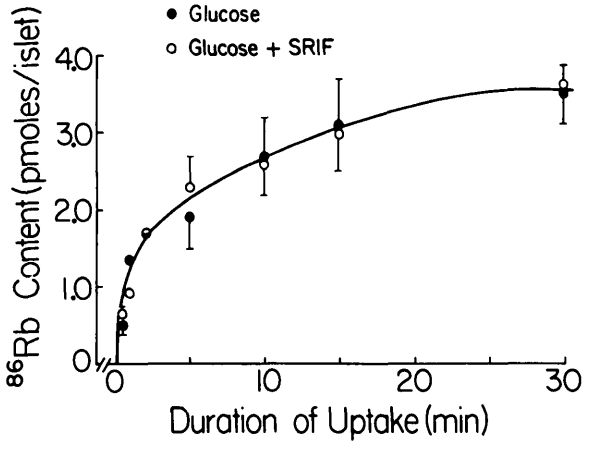


FIGURE 3. Effect of SRIF in the presence of glucose on ^{86}Rb accumulation in cultured rat islet cells. The uptake of ^{86}Rb in excess of the ^{3}H-sucrose space was determined in the presence of 16.7 mM glucose (—●—) or 16.7 mM glucose plus 100 ng/ml SRIF (—○—). Each point and the vertical bar represents the mean ± SE of 3–5 individual observations.

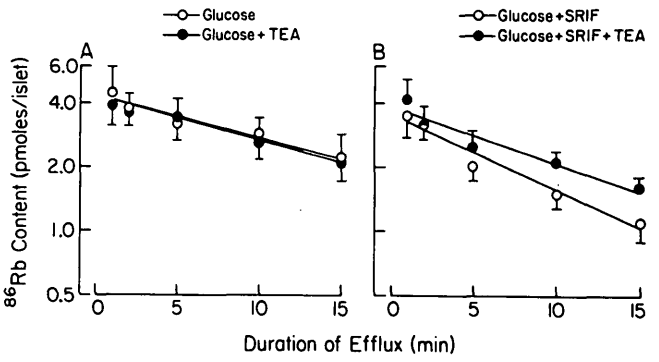


FIGURE 5. Effect of TEA on the rate of ^{86}Rb efflux from cultured rat islets in the presence of glucose and SRIF. The data represent the ^{86}Rb content of the islets in excess of the ^{3}H-sucrose space. Glucose (16.7 mM) was present in all experiments shown in A and B, and 20 mM TEA and/or 100 ng/ml SRIF were added as indicated. Each value with the vertical bar represents the mean ± SE of at least 10 observations. The solid lines are single exponential curve fits obtained by the method of least squares.

mentation of the increase in ^{86}Rb efflux (Table 4). Raising K^+ from 5 to 13 mM also led to an increase in ^{86}Rb efflux, but the addition of SRIF to a medium containing excess K^+ did not produce a further increase in the efflux rate (Table 4).

DISCUSSION

The study of the mode of action of SRIF provides an excellent opportunity to establish the relative importance of selected cellular phenomena in contributing to the physiologic regulation of insulin release from the β-cell. The primary effect of SRIF may be to disrupt the transduction of molecular information at the level of the plasma membrane via the activity of adenylate cyclase and components controlling Ca^{2+} and K^+ permeabilities.[1]

The suggestion that SRIF disrupts plasma membrane activation of Ca^{2+} permeability has stemmed from evidence showing that elevation of the concentration of extracellular Ca^{2+} or K^+ antagonizes the inhibitory action of SRIF.[1,6,8,27–31] The antagonistic action of high K^+ on SRIF inhibition of glucose-induced insulin release may be due to depolarization and subsequent activation of voltage-dependent Ca^{2+} channels.[1,32,33] Because an increase in extracellular Ca^{2+} in the presence of high glucose is associated with an increase in $^{45}Ca^{2+}$ uptake,[34] it seems reasonable to conclude that the antagonistic influence of excess Ca^{2+} on the action of SRIF is primarily due to an increase in Ca^{2+} uptake, as has been documented by several investigators.[4,6,7] This suggests that SRIF interferes with stimulation of Ca^{2+} entry into the β-cell, rather than blocking a Ca^{2+}-dependent site distal to plasma membrane associated processes, a concept that is further supported by the observation that SRIF inhibits glucose-induced electrical activity in islet cells. It is generally accepted that the spike activity in β-cells is due mostly to voltage-dependent Ca^{2+} influx,[32,33,35,36] although this point is still under investigation.[37] Partial reversal of the inhibitory action of SRIF on glucose-induced electrical and secretory events occurs by adding excess Ca^{2+} or K^+,[1,8] or the drugs TEA or quinine, suggesting that the primary action of SRIF may be to increase the P_K of the plasma membrane, thus shifting the membrane potential toward the K^+ equilibrium potential. The membrane may then hyperpolarize to a level beyond the threshold for elicitation of voltage-dependent Ca^{2+} spikes. The depolarization of the β-cell membrane associated with glucose-induced insulin release appears to be primarily due to a reduction in P_K.[10,11,13,14,20–22,26,38] The regulation of P_K has an important role in the maintenance of the oscillatory pattern of electrical activity evoked by glucose.[9,11,13,39] Prevention of an increase in P_K inhibits repolarization to the silent phase, producing continuous spike activity.

It is not clear as to the mechanism by which SRIF, in the presence of TEA and glucose, elicits silent phases followed by depolarization with superimposed spikes (Figure 2, cell 1). A possible explanation may be that SRIF by activation of P_K counteracts, in a phasic manner, the inhibitory influence of TEA on P_K. However, we have often observed that SRIF induces instability in the membrane potential and pattern of spike activity, and this suggests that the hormone alters ionic control mechanisms subserving the oscillatory nature of the spike activity.

The results of the ^{86}Rb accumulation studies indicate that SRIF may not hyperpolarize the plasma membrane via activation of a Na-K ATPase, since there is no difference ob-

FIGURE 4. Influence of SRIF on the rate of ^{86}Rb efflux from cultured rat islet cells exposed to low or high glucose. The data represent the ^{86}Rb content of the islets in excess of the ^{3}H-sucrose space. Each value with the vertical bar represents the mean ± SE of at least 10 observations. The solid lines are single exponential curve fits obtained by the method of least squares.

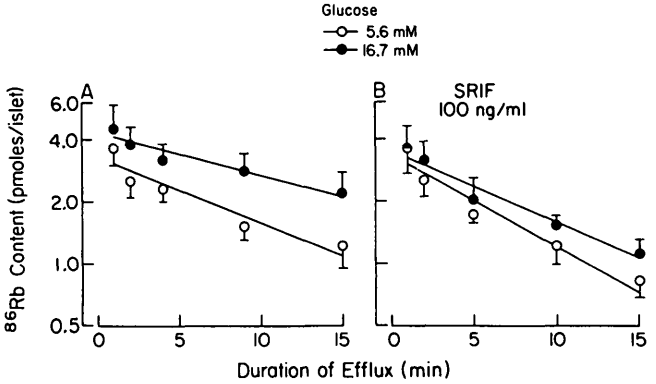


TABLE 4
Influence of quinine, Ca^{2+}, and K^+ on rate of ^{86}Rb efflux in the presence of glucose and/or somatostatin*

Experiment	Addition	Glucose (16.7 mM)	SRIF (100 ng/ml)	^{86}Rb content after 15 min (pmol/islet)
A 1	Control	+	−	2.1 ± 0.28 (13)
2		+	+	1.1 ± 0.17 (13)
B 1	Quinine, 0.1 mM	+	−	2.4 ± 0.25 (6)
2		+	+	1.7 ± 0.09 (4)
C 1	Ca^{2+}, 5 mM	+	−	0.9 ± 0.07 (8)
2		+	+	0.7 ± 0.05 (6)
D 1	K^+, 13 mM	+	−	1.6 ± 0.13 (12)
2		+	+	1.7 ± 0.18 (5)

* The values represent the ^{86}Rb content of islets, preloaded with ^{86}Rb and ^3H-sucrose, after 15 min of exposure to radioisotope-free medium containing the indicated agents. Each value is the mean ± SE of the number of experiments indicated in parenthesis. The following are P values indicating the statistical significance of the secretory response in relation to a control value. NS indicates not significant.

<0.005	<0.01	<0.03	NS
A_2 vs. A_1	B_2 vs. A_2	B_2 vs. B_1	B_1 vs. A_1
		D_2 vs. A_2	B_2 vs. B_1
			C_2 vs. C_1
			D_1 vs. A_1
			D_2 vs. D_1
			D_2 vs. A_1

served in the rate of ^{86}Rb uptake in the presence of glucose vs. glucose plus SRIF. It is clearly evident from the ^{86}Rb efflux studies that SRIF enhances P_K, thereby antagonizing the glucose-induced decrease in P_K. Both antagonists of P_K activation, TEA or quinine, effectively counteracted the SRIF-induced augmentation of ^{86}Rb efflux, lending further supporting evidence to a possible direct action of SRIF on P_K.

The definitive effects of SRIF on the inhibition of Ca^{2+} uptake on one hand,[4,6,7] and the augmentation of ^{86}Rb efflux on the other, suggest that one or both of these phenomena prevent normal regulation of a Ca^{2+}-sensitive P_K system. The influence of excess Ca^{2+} on ^{86}Rb efflux is consistent with electrophysiologic studies that revealed the dynamic relationship between changes in Ca^{2+} and K^+ permeabilities.[9] These studies showed that an increase in the Ca^{2+} level from 2.5 to 5.0 mM in the presence of 11.1 mM glucose elicited prolonged silent phases between bursts of spikes at a potential more negative than that obtained in the presence of 2.5 mM Ca^{2+}. We have observed a similar effect of excess Ca^{2+} on the membrane potential in previous studies in which cultured rat islet cells were used.[1] Although excess Ca^{2+} led to hyperpolarization and a decrease in the level of spike activity in the cultured islet cells, the addition of SRIF led to no further change in these parameters. The inability of excess Ca^{2+} to reverse the influence of SRIF on either the membrane potential or the rate of ^{86}Rb efflux is probably due to activation of a Ca^{2+}-sensitive P_K. Other investigators have found that excess K^+ increases the rate of ^{86}Rb efflux in the presence of high glucose.[23] The increase in ^{86}Rb efflux with high K^+ may be due to activation of a Ca^{2+}-sensitive P_K resulting from a K^+-induced increase in Ca^{2+} uptake.[40]

The ability of SRIF to provoke only a transient hyperpolarization and a decrease in the frequency of the generation of bursts of electrical activity in microdissected mouse islets contrasts with the sustained inhibitory influence of SRIF on electrical events in cultured rat islet cells.[1] This may be due to a greater sensitivity of cultured rat islet cells to SRIF, or to the alteration in the topography of the islet cells and, thereby, impairment of the paracrine influence of intraislet hormonal release.

In view of the hypothesis that a signal stemming from glucose metabolism serves as a trigger for both the membrane and the secretory events,[41] it is important to determine if the action of SRIF could be mediated by inhibition of glucose metabolism. Our previously reported findings[1] are in agreement with other studies in which SRIF was found not to affect the metabolism of glucose through the glycolytic pathway,[2] the Krebs cycle,[5,42] or the pentose monophosphate shunt.[2,5] In light of these results, it is apparent that SRIF can influence processes involved in the transduction of glucose activation without the mediating influence of glucose metabolism.

In summary, evidence from electrophysiologic and cationic flux studies indicates that SRIF-induced hyperpolarization is most likely due to an increase in P_K to an extent that counteracts the decrease in P_K elicited by high glucose. Consequently, in the absence of adequate depolarization, the influx of Ca^{2+} via voltage-sensitive Ca^{2+} channels would be inhibited as indicated by the inhibition of spike activity and ^{45}Ca uptake. The ability of TEA or quinine to antagonize the influence of SRIF on electrical events, insulin release, and ^{86}Rb efflux supports the postulate that the peptide activates P_K as its primary mode of action. It may be concluded that SRIF inhibits the transduction of secretory information at the level of the cell membrane by increasing and decreasing K^+ and Ca^{2+} permeabilities, respectively, and directly or indirectly (via reduction of $\{Ca^{2+}\}_i$) inhibiting the activity of adenylate cyclase.[1] This would interrupt the coupling of the recognition process to activation of the secretory complex. This postulated mechanism of action is attractive in view of the widespread inhibitory action of SRIF in its role as a regulatory chemical messenger for a wide variety of secretory cells.

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