

# Two Generations of Insulinotropic Imidazoline Compounds

Suad Efendic,<sup>1</sup> Alexander M. Efanov,<sup>1</sup> Per-Olof Berggren,<sup>1</sup> and Sergei V. Zaitsev<sup>1,2</sup>

**The imidazoline RX871024 increased basal- and glucose-stimulated insulin release in vitro and in vivo. The compound inhibited activity of ATP-sensitive K<sup>+</sup> channels as well as voltage-gated K<sup>+</sup> channels, which led to membrane depolarization, an increase in the cytosolic Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>i</sub>), and insulin release. Importantly, RX871024 also enhanced the insulinotropic effect of glucose in cells with clamped [Ca<sup>2+</sup>]<sub>i</sub> but in the presence of high ATP and Ca<sup>2+</sup> concentration inside the cell. We believe that the latter effect on insulin exocytosis was at least in part mediated by a rise in diacylglycerol, which then activated protein kinase C (PKC) and increased the generation of arachidonic acid (AA) metabolites. Activation of both the PKC and AA pathways resulted in potentiation of glucose effects on insulin secretion. Unlike RX871024, the novel imidazoline BL11282 did not block ATP-dependent K<sup>+</sup> channels, but similarly to RX871024, it stimulated insulin secretion in depolarized or permeabilized islets. Accordingly, BL11282 did not influence glucose and insulin levels under basal conditions either in vitro or in vivo, but it markedly enhanced the insulinotropic effects of glucose. BL11282 restored the impaired insulin response to glucose in islets from spontaneously diabetic GK rats. We conclude that BL11282 belongs to a new class of insulinotropic compounds that demonstrate a strong glucose-dependent effect on insulin exocytosis. *Diabetes* 51 (Suppl. 3):S448–S454, 2002**

**G**lucose stimulates insulin secretion mainly by activation of two mechanisms: increasing the cytosolic Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>i</sub>) (1) and directly promoting insulin exocytosis (2). It has been demonstrated that sulfonylureas increase insulin secretion by simulating the effect of glucose on [Ca<sup>2+</sup>]<sub>i</sub> (3). However, recent data suggest that sulfonylureas also mod-

erately enhance the direct effect of glucose on exocytosis (4,5). The direct insulinotropic effect of sulfonylureas, observed already at normal or moderately increased blood glucose concentrations, may provoke pronounced and prolonged hypoglycemia in patients treated with these drugs (6). Therefore, drugs that solely enhance the exocytotic component of the insulinotropic effect of glucose by influencing transport and fusion of insulin granules could provide a better alternative to sulfonylureas in treatment of type 2 diabetes. It has been shown that glucagon like peptide-1 (GLP-1), a peptide from the gut, shows a glucose-dependent insulinotropic effect and exerts a strong antidiabetic effect (7). However, the necessity of injecting this peptide during the treatment led to the idea to search for small organic compounds possessing glucose-dependent insulinotropic activity similar to GLP-1. Among those compounds, of special interest are novel imidazoline compounds (8,9).

Phentolamine, an  $\alpha$ -adrenergic blocking agent with an imidazoline ring, stimulated basal and glucose-induced insulin release in humans and animals (10–12). These data were initially interpreted as an indication of the important role of  $\alpha_2$ -adrenergic receptors in the regulation of insulin release, even under nonstress conditions. Subsequently, we have demonstrated that the more selective  $\alpha_2$ -adrenergic blocking agent idazoxan does not enhance basal or glucose-stimulated insulin release. Therefore, we proposed that the stimulatory effect of phentolamine on insulin release could not be accounted for by its action on  $\alpha_2$ -adrenoceptors, but to the effect of the compound on other sites (13,14). Similarly, others have shown that imidazoline substances increased insulin release after irreversible blockade or downregulation of  $\alpha_2$ -adrenoceptors, and they proposed that the stimulatory effect of the compounds on insulin release was probably related to their imidazoline moiety (15–17). Importantly, some imidazoline compounds exerted a strong effect on the exocytotic component of the insulinotropic effect of glucose (8,18). Furthermore, several imidazolines have already shown promising antihyperglycemic effects in animal models of diabetes and in human subjects (19–21).

In this review, we concentrate on our studies exploring the mechanisms of the insulinotropic effect of two groups of imidazoline compounds:

- classical insulinotropic imidazolines, i.e., imidazoline derivatives possessing both ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channel activity and a direct effect on exocytosis, and
- a new generation of imidazoline compounds without effects on K<sub>ATP</sub> channels and possessing a pure glucose-dependent insulinotropic activity.

From the <sup>1</sup>Rolf Luft Center for Diabetes Research, Department of Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; and the <sup>2</sup>Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, Russia.

Address correspondence and reprint requests to Sergei V. Zaitsev, The Rolf Luft Center for Diabetes Research, Department of Molecular Medicine, Karolinska Institutet, Karolinska Hospital, L3, SE-171 76 Stockholm, Sweden. E-mail: sergei.zaitsev@molmed.ki.se.

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A.M.E. is currently affiliated with Lilly Forshung, Lilly Research Laboratories, Hamburg, Germany.

AA, arachidonic acid; [Ca<sup>2+</sup>]<sub>i</sub>, cytosolic Ca<sup>2+</sup> concentration; CCh, carbamylcholine; DAG, diacylglycerol; K<sub>ATP</sub>, ATP-sensitive K<sup>+</sup> channel; K<sub>Ca</sub>, Ca<sup>2+</sup>-dependent potassium channel; K<sub>DR</sub>, delayed rectifier potassium channel; MB-1-ABT, methylbenzyl-1-aminobenzotriazole; PA, phosphatidic acid; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

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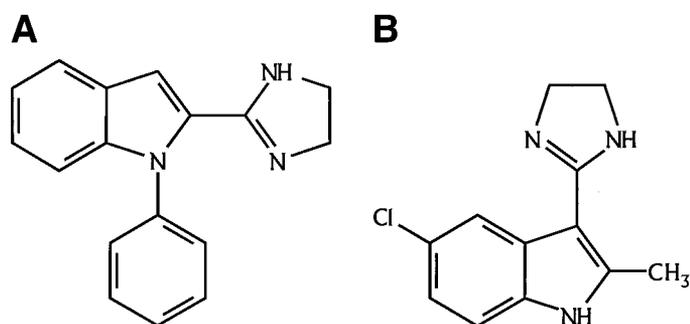


FIG. 1. The structures of imidazoline compounds RX871024 (A) and BL11282 (B).

**Classical insulinotropic imidazolines, i.e., imidazoline derivatives possessing both  $K_{ATP}$  channel activity and a direct effect on exocytosis**

**Stimulation of insulin secretion by the imidazoline compound RX871024.** In rat pancreatic islets, the stimulation of insulin secretion by low concentrations (5 and 10  $\mu\text{mol/l}$ ) of RX871024 (Fig. 1A) was highly glucose-dependent (Fig. 2) (18). At basal glucose (3.3 mmol/l), these concentrations of the compound had only a modest insulinotropic effect, whereas at 16.7 mmol/l glucose, 10  $\mu\text{mol/l}$  RX871024 exerted an up to fourfold increase in insulin secretion. Higher concentrations of the compound stimulated insulin secretion at both basal and elevated glucose concentrations. The marked sensitizing effect of low doses of RX871024 on glucose-induced insulin secretion suggested that imidazoline compounds of this type may constitute the basis for the development of a new therapeutic concept in the treatment of diabetes. These new therapeutic agents should not initiate insulin secretion per se, but rather work synergistically with elevated glucose concentrations.

**Effects of RX871024 on  $[Ca^{2+}]_i$  in the  $\beta$ -cell.** RX871024 increased  $[Ca^{2+}]_i$  in pancreatic  $\beta$ -cells (18). This elevation in  $[Ca^{2+}]_i$  was dependent on concentrations of both the compound and glucose and was only observed in the presence of extracellular  $Ca^{2+}$ .

The increase in  $[Ca^{2+}]_i$  produced by RX871024 was mediated through membrane depolarization and subse-

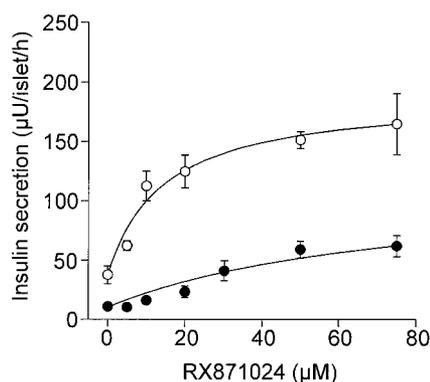


FIG. 2. Stimulation of insulin secretion by RX871024 in the presence of 3.3 (●) and 16.7 (○) mmol/l glucose. Insulin secretion was measured in Wistar rat pancreatic islets. Data are means  $\pm$  SE from six experiments. (Copyright 1996 American Diabetes Association. From *Diabetes* Vol. 45, 1996, p. 1610–1618. Reprinted with permission from the American Diabetes Association.)

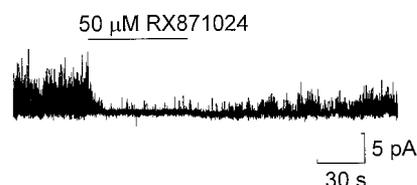


FIG. 3. RX871024 inhibits truncated Kir6.2 channel expressed in *Xenopus* oocytes. Representative trace of three separate experiments. (Copyright 2001 by Academic Press. From *Biochem Biophys Res Comm* Vol. 284, 2001, p. 918–922. Reprinted with permission from Academic Press.)

quent opening of voltage-gated  $Ca^{2+}$  channels. RX871024 depolarized the membrane by blocking  $K^+$  channels in pancreatic  $\beta$ -cells.  $K_{ATP}$ ,  $Ca^{2+}$ -dependent potassium ( $K_{Ca}$ ), and delayed rectifier potassium ( $K_{DR}$ ) channels were all inhibited upon addition of the compound (18). In contrast to glibenclamide, which inhibited  $K_{ATP}$  channel activity by binding to the sulfonylurea receptor-1 subunit of the channel, RX871024 interacted with Kir6.2, the pore-forming channel subunit (22). Application of the imidazoline blocked the conductance of truncated Kir6.2 $\Delta$ C26 expressed in *Xenopus laevis* oocytes (Fig. 3). These data are consistent with the observation that another imidazoline compound, phentolamine, blocked Kir6.2 $\Delta$ C26 activity (23). After inhibition of  $K^+$  conductance and membrane depolarization, voltage-dependent  $Ca^{2+}$  channels were activated, leading to rises in  $[Ca^{2+}]_i$  and exocytosis of insulin-containing secretory granules.

**Activity of protein kinase A and C and the insulinotropic effect of RX871024.** The effects of the imidazoline RX871024 on insulin secretion were also studied under conditions in which  $[Ca^{2+}]_i$  was kept constant (18,24). Islets were either depolarized with high concentrations of KCl and glucose or electroporated. Despite the lack of  $[Ca^{2+}]_i$  increase, RX871024 stimulated insulin secretion. This insulinotropic effect of imidazoline, independent from changes in  $[Ca^{2+}]_i$ , required a moderately high constant level of  $Ca^{2+}$  inside the cell and a high-energy state of the cell. The observed stimulation of insulin release under these conditions likely involved activation of protein kinases. First, inhibitors of protein kinase A (PKA) (H-89 and Rp-BrcAMPS) or protein kinase C (PKC) (calphostin C and staurosporine) completely abolished imidazoline-induced increases in insulin secretion, whereas glucose- and KCl-induced stimulation of insulin secretion were unaffected (18). Second, measurements of protein phosphorylation in permeabilized insulin-secreting HIT T15 cells show that RX871024 induced protein phosphorylation (24). Finally, the increase in phosphorylation induced by the imidazoline was blocked by the protein kinase inhibitors Rp-BrcAMPS, H-89, and staurosporine (24). Thus, the imidazoline RX871024 induced insulin secretion not only by depolarizing the membrane and increasing  $[Ca^{2+}]_i$ , but also by stimulating PKA- and PKC-dependent protein phosphorylation in pancreatic  $\beta$ -cells. The second messengers regulating activity of PKA and PKC are cAMP and diacylglycerol (DAG), respectively. Effects of RX871024 on concentrations of cAMP were measured in rat pancreatic islets (18). In our experiments, RX871024 did not influence the concentration of cAMP, which suggests that PKA activity probably plays a permissive role in stimulation of insulin secretion and protein phosphorylation by the imi-

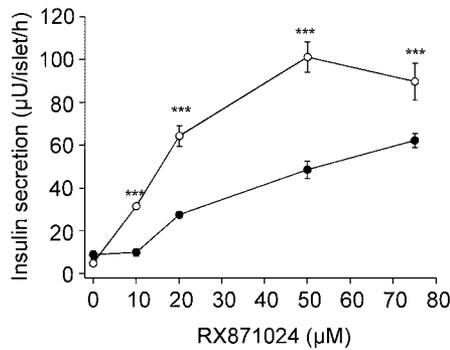


FIG. 4. Potentiation of RX871024 induced insulin secretion by dibutyryl-cAMP. Insulin secretion was measured in isolated Wistar rat pancreatic islets in the presence of 3.3 mmol/l glucose in the absence (●) and in the presence (○) of 4 mmol/l dibutyryl-cAMP ( $n = 12$ ). \*\*\* $P < 0.001$  vs. insulin secretion in the absence of dibutyryl-cAMP.

dazoline. This notion was supported by experiments demonstrating synergism between effects of RX871024 and a cell-permeable cAMP analog, dibutyryl-cAMP, on insulin secretion (Fig. 4).

**RX871024 increased DAG levels in rat pancreatic islets.** Measurements of DAG levels in rat pancreatic islets demonstrated that 50 µmol/l RX871024 induced a twofold increase in DAG concentration (Fig. 5) (25). The same amplitude of DAG increase was reached with an agonist of muscarinic receptors that activates phospholipase C (PLC), 200 µmol/l carbamylcholine (CCh). A combination of both compounds resulted in an additive effect on DAG levels. CCh has been used at concentration, which maximally stimulates insulin secretion (26).

It was reported that  $I_1$  ligands increased DAG production in neurons through activation of phosphatidylcholine-specific PLC (27,28). We used an inhibitor of this PLC isozyme, D609, to examine whether the effect of RX871024 on DAG concentration was mediated through a similar mechanism. D609 did not block elevation of DAG induced by the imidazoline. Thus, RX871024 induced an increase in

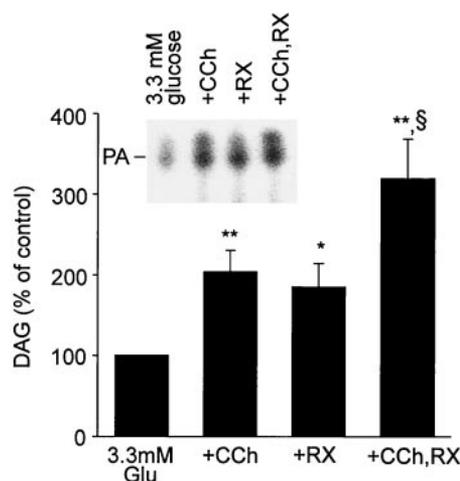


FIG. 5. Effects of 200 µmol/l CCh and 50 µmol/l RX871024 on DAG concentration in Wistar rat islets. DAG was phosphorylated to PA with DAG kinase in the presence of  $^{32}P$ - $\gamma$ -ATP. After thin-layer chromatography separation, autoradiography of the area corresponding to PA was performed. \* $P < 0.05$ , \*\* $P < 0.01$  vs. DAG level at basal conditions; § $P < 0.05$  vs. DAG level at 50 µmol/l RX871024. Glu, glucose; RX, RX871024. (Copyright 2001 by Academic Press. From *Biochem Biophys Res Comm* Vol. 281, 2001, p. 1070–1073. Reprinted with permission from Academic Press.)

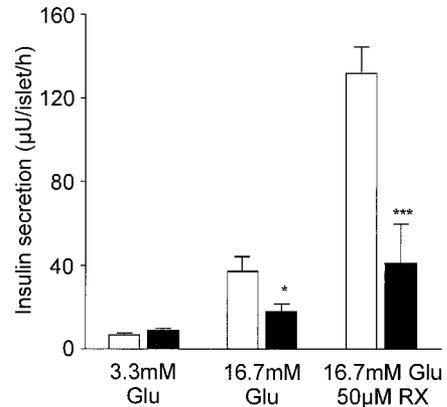


FIG. 6. Effects of MB-1-ABT, a P-450 inhibitor, on insulin secretion induced by glucose and RX871024 in isolated Wistar rat islets. Islets were preincubated for 30 min with (■) or without (□) 200 µmol/l MB-1-ABT ( $n = 11$ ). \* $P < 0.05$ , \*\*\* $P < 0.01$  vs. insulin secretion in the absence of MB-1-ABT. Glu, glucose; RX, RX871024.

DAG concentration in pancreatic islets by mechanisms distinct from activation of phosphatidylcholine-specific PLC. Additionally, these mechanisms did not involve phosphatidylinositol-specific PLC activation through muscarinic receptors because RX87104 and CCh had an additive effect on DAG concentration.

The mechanism behind the imidazoline-induced increase in DAG concentration could involve alternative steps in production and/or degradation of DAG, such as de novo DAG synthesis or conversion of DAG to phosphatidic acid (PA). It is well established that in pancreatic islets DAG can be synthesized from glucose (29). DAG can be converted back to PA by DAG kinase. To date, nine DAG kinase isozymes have been cloned showing tissue-specific distribution (30). However, there are no data on DAG kinase characterization in  $\beta$ -cells.

The effects of RX871024 and CCh on DAG levels were further compared with the effects of these compounds on insulin secretion in rat pancreatic islets (25). At 3.3 mmol/l glucose, 10–50 µmol/l RX871024 induced insulin secretion, with a maximal stimulation of 500%. However, 200 µmol/l CCh induced only a twofold increase in insulin secretion. A combination of RX871024 and CCh produced an 11-fold stimulation of insulin secretion. In all cases, D609 did not affect insulin secretion induced by the individual compounds or their combination.

Elevation of DAG levels by the imidazoline RX871024 likely plays a significant role in imidazoline-induced insulin secretion, in particular in the component independent of  $[Ca^{2+}]_i$  changes. DAG may affect a number of targets important in the regulation of insulin secretion. One such target is PKC. Activation of PKC by a number of stimuli leads to stimulation of insulin secretion without concomitant elevation in  $[Ca^{2+}]_i$  (31). RX871024-mediated potentiation of insulin secretion is dependent on PKC activation. Another possible role for DAG generated by the imidazoline compound is generation of arachidonic acid (AA) and its metabolites. DAG is used as a substrate for the generation of AA in a process mediated by DAG lipase, the activity of which is important for glucose-induced insulin secretion (32). AA can be metabolized by cyclooxygenase to prostaglandins and related compounds, by lipoxygenases to leukotrienes, and by cytochrome P-450 enzymes to

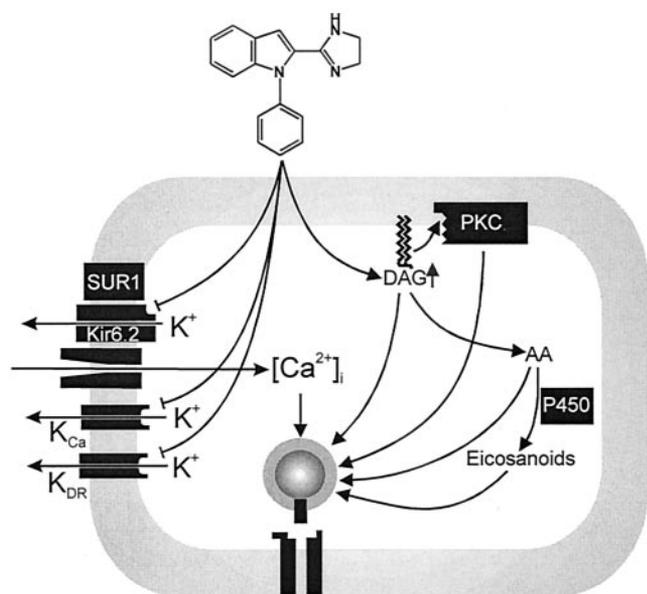


FIG. 7. Molecular mechanisms of insulintropic activity of imidazoline compound RX871024. SUR1, sulfonylurea receptor 1.

epoxyeicosatrienoic acids (33). Cytochrome P-450 generated epoxyeicosatrienoic acids have been shown to play a role in insulin secretion (34). We have studied the effects of the cytochrome P-450 inhibitor methylbenzyl-1-aminobenzotriazole (MB-1-ABT) (35) on insulin secretion induced by glucose and RX871024 (Fig. 6). Incubation with 200  $\mu\text{mol/l}$  MB-1-ABT inhibited glucose-induced insulin secretion and suppressed imidazoline-induced potentiation of glucose-induced insulin secretion. These data suggest that AA metabolites contributed to the insulintropic activity of the imidazoline RX871024.

In conclusion, the imidazoline compound RX871024 promotes insulin release in the pancreatic  $\beta$ -cell through interaction with several molecular targets (Fig. 7). First, it inhibits the  $K_{\text{ATP}}$  channel as well as  $K_{\text{Ca}}$  and  $K_{\text{DR}}$  channels, which leads to membrane depolarization, activation of voltage-gated  $\text{Ca}^{2+}$  channels, and increased  $[\text{Ca}^{2+}]_i$ . High  $\text{Ca}^{2+}$  concentrations inside the cell then trigger fusion of insulin-containing granules with the plasma membrane. Second, RX871024 potentiates insulin exocytosis under conditions where membrane potential and  $[\text{Ca}^{2+}]_i$  are kept constant. This effect of imidazoline involves activation of

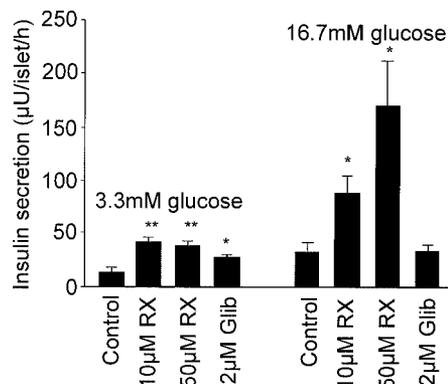


FIG. 8. Effects of RX871024 (RX) and glibenclamide (Glib) on insulin secretion from isolated human islets ( $n = 5$ ). \* $P < 0.05$ , \*\* $P < 0.01$  vs. insulin secretion in the absence of the compounds.

protein phosphorylation and is most likely mediated by an increase in DAG concentration inside the cell. Elevated DAG levels activate PKC and increase concentrations of AA and its metabolites, which in turn leads to stimulation of exocytosis.

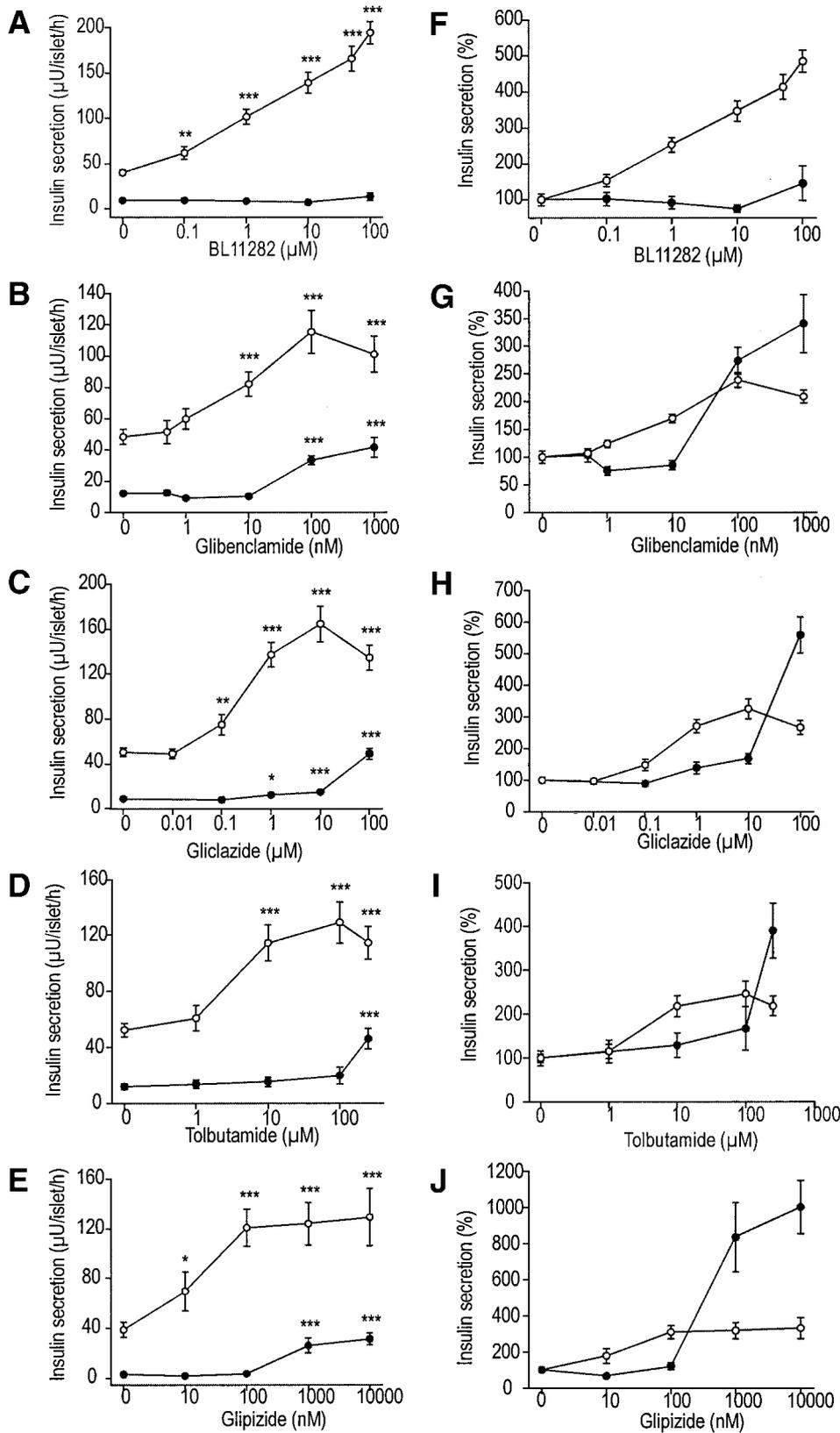
**Insulintropic activity of the imidazoline RX871024 in human islets.** Insulintropic activity of RX871024 was also examined in isolated human pancreatic islets (Fig. 8). Incubation with 10 and 50  $\mu\text{mol/l}$  RX871024 induced a 300% increase in insulin secretion at 3.3 mmol/l glucose, whereas at 16.7 mmol/l glucose, 200 and 400% increases were observed with 10 and 50  $\mu\text{mol/l}$  RX871024, respectively. RX871024 produced a much higher stimulation of insulin secretion than the sulfonylurea glibenclamide. Also, 2  $\mu\text{mol/l}$  glibenclamide produced a twofold stimulation of insulin secretion at 3.3 mmol/l glucose and was ineffective at 16.7 mmol/l glucose.

**Effect of the imidazoline compound RX871024 on pancreatic  $\alpha$ - and  $\delta$ -cells.** Diabetic patients exhibit decreased insulin and somatostatin release (36–38). At the same time, glucagon levels are often elevated, leading to hyperglycemia (39,40). The suppression of glucagon release results in decreased hepatic glucose production (41,42), whereas enhanced somatostatin release prolongs the rate of absorption of nutrients and attenuates hyperglycemia (43).

The ideal profile for an antidiabetic drug would be one that possesses both the ability to stimulate insulin and somatostatin secretion and the capacity to reduce glucagon release. Indeed, RX871024 exerts a complex effect on the endocrine pancreas by stimulating arginine-induced insulin and somatostatin release and inhibiting glucagon release. In isolated perfused Wistar rat pancreas, RX871024, at a concentration of 10  $\mu\text{mol/l}$ , had no effect on basal hormone secretion (3.3 mmol/l glucose). However, when the pancreas was stimulated with L-arginine (20 mmol/l), RX871024 significantly enhanced both the first and second phases of arginine-stimulated insulin and somatostatin secretion (44). Moreover, 10  $\mu\text{mol/l}$  RX871024 significantly inhibited both phases of arginine-induced glucagon release, and at a concentration of 1  $\mu\text{mol/l}$ , it suppressed the second phase of arginine-induced glucagon release (44).

The stimulatory effects of RX871024 on insulin secretion can be explained by an inhibition of  $K_{\text{ATP}}$  channel activity, leading to membrane depolarization, with the subsequent opening of voltage-gated L-type  $\text{Ca}^{2+}$  channels, increasing  $[\text{Ca}^{2+}]_i$  and resulting in insulin release. The stimulation of somatostatin secretion by RX871024 can also be explained by an inhibition of  $K_{\text{ATP}}$  channel activity because a key role for  $K_{\text{ATP}}$  channels in the regulation of somatostatin release from pancreatic  $\delta$ -cells has been shown (45,46).

What is the mechanism of RX871024-induced inhibition of glucagon release? It is speculated that insulin and somatostatin released from  $\beta$ - and  $\delta$ -cells, respectively, inhibit glucagon release from  $\alpha$ -cells via intraislet interactions (47). Also, the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid, cosecreted with insulin from  $\beta$ -cells, may mediate the inhibition of glucagon secretion (48). However, a low dose (1  $\mu\text{mol/l}$ ) of RX871024 inhibited glucagon secretion without any significant influence on insulin and somatostatin release. These data do not favor the idea that RX871024-mediated suppression of arginine-induced

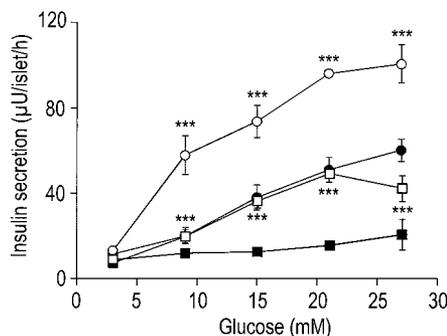


**FIG. 9.** Effects of the imidazoline compound, BL11282 (A and F) or the sulfonylureas glibenclamide (B and G), gliclazide (C and H), tolbutamide (D and I), and glipizide (E and J) on insulin secretion in isolated Wistar rat pancreatic islets at 3.3 (●) and 16.7 (○) mmol/l glucose. In F–J, insulin secretion was expressed as the percent of increase over insulin secretion at the corresponding glucose concentration, without the addition of compounds (100% insulin secretion in the presence of 3.3 or 16.7 mmol/l glucose). \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001 vs. insulin secretion in the absence of the compounds. (Copyright 2001 American Diabetes Association. From *Diabetes* Vol. 50, 2001, p. 797–802. Reprinted with permission from the American Diabetes Association.)

glucagon release is due to a paracrine action by insulin and somatostatin on the  $\alpha$ -cells. For this reason, a direct inhibitory effect of RX871024 on glucagon secretion is more likely.

**A new generation of imidazoline compounds without effects on  $K_{ATP}$  channels and possessing a pure glu-**

**case-dependent insulinotropic activity.** The search for imidazoline compounds possessing only the effect on exocytosis resulted in the development of a novel compound, BL11282 (Fig. 1B) (8). BL11282 did not block the activity of  $K_{ATP}$  channels, as assessed in the perforated whole-cell configuration of the patch-clamp technique (8).



**FIG. 10.** Dose-response curves for glucose effects on insulin secretion in isolated pancreatic islets from Wistar and GK rats. Dose-response curves were obtained in the presence of 50  $\mu\text{mol/l}$  BL11282 ( $\circ$ , Wistar;  $\square$ , GK) or without the drug ( $\bullet$ , Wistar;  $\blacksquare$ , GK).  $***P < 0.001$  vs. insulin secretion at 3 mmol/l glucose. (Copyright 2001 American Diabetes Association. From *Diabetes* Vol. 50, 2001, p. 797–802. Reprinted with permission from the American Diabetes Association.)

As a result of its incapacity to inhibit  $K_{\text{ATP}}$  channels in intact cells, BL11282 did not influence insulin secretion at 3.3 mmol/l glucose in isolated Wistar rat pancreatic islets (Fig. 9A and F). An increase in the ambient glucose concentration to 16.7 mmol/l resulted in a potent stimulatory effect of BL11282 on insulin secretion. The compound potentiated glucose-induced insulin secretion at a concentration range of 0.1–100  $\mu\text{mol/l}$ , and the maximum stimulation was  $\sim 500\%$  of the level of glucose-induced insulin secretion in the absence of the compound. The concentration of BL11282 giving the half-maximum effect ( $\text{EC}_{50}$ ) on glucose-induced insulin secretion was  $1.3 \pm 0.4 \mu\text{mol/l}$ . In contrast to BL11282, all of the sulfonylureas tested, i.e., glibenclamide (Fig. 9B and G), gliclazide (Fig. 9C and H), tolbutamide (Fig. 9D and I), and glipizide (Fig. 9E and J), showed stimulation of insulin secretion at both basal and elevated glucose concentrations. Folds of the increases in insulin secretion induced by sulfonylureas over the insulin secretion induced by glucose alone were higher in the presence of 3.3 mmol/l glucose than in the presence of 16.7 mmol/l glucose (Fig. 9G–J).

The glucose dependency of the stimulation of insulin secretion by BL11282 was also observed in pancreatic islets from diabetic rats (Fig. 10). Interestingly, despite the failure of glucose alone to stimulate insulin secretion in islets from diabetic rats, the combination of glucose with BL11282 led to complete recovery of the stimulatory effect of glucose to the levels observed in control islets. This effect was similar to that observed with RX871024 (49). However, in contrast to RX871024, the compound BL11282 had no effect on basal insulin release.

The imidazoline BL11282 potentiated insulin secretion without concomitant changes in  $[\text{Ca}^{2+}]_i$  in islets either depolarized with 55 mmol/l KCl and 16.7 mmol/l glucose or electropermeabilized (49). These effects of BL11282, as well as their dependence on the activation of protein kinases A and C, are similar to the effects of RX871024 on insulin exocytosis (18,24).

Thus, in this study we discuss for the first time a new imidazoline compound that stimulates insulin secretion only if the glucose concentration is elevated from the basal level. The administration of this compound did not decrease the blood glucose concentration under the basal

conditions. Hence, the risk for hyperglycemia with this type of compound is negligible.

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