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HYPOGLYCEMIC ACTIVITY OF *l*-α-(3,4-DIMETHOXYPHENETHYLAMINOMETHYL)-2-HYDROXYBENZYLALCOHOL 1/2 FUMARATE (TA-078) IN THE MOUSE, RAT AND DOG

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Abstract—*l*-α-(3,4-Dimethoxyphenethylaminomethyl)-2-hydroxybenzylalcohol 1/2 fumarate (TA-078) is a new hypoglycemic agent structurally different from any existing hypoglycemic drug. It depresses the rise of blood glucose when it is orally administered to glucose-loaded mice, rats and beagle dogs at minimal doses of 1, 10 and 2.5 mg/kg, respectively. In contrast with tolbutamide, TA-078 hardly affected fasting blood glucose levels in rats and dogs and only weakly reduced fasting blood glucose levels in mice. Oral administration of TA-078 to KK mice also improved glucose tolerance, while no improvement was observed in streptozotocin-diabetic rats. TA-078 elevated plasma immunoreactive insulin (IRI) levels in mice and rats soon after its oral administration. In fasted rats, TA-078 caused only a transient increase in plasma IRI but did not affect plasma immunoreactive glucagon (IRG) levels in the early phase after its administration. On the other hand, tolbutamide induced a sustained increase in plasma IRI and a transient but marked decrease in plasma IRG. In perfused rat pancreas, TA-078 stimulated insulin secretion. The stimulation by 10 μg/ml TA-078 in the perfusion liquid required the presence of a normal concn (5.6 mM) of glucose, whereas the same concn of tolbutamide stimulated insulin release even at a low glucose concn (2.8 mM).

Oral hypoglycemic drugs such as sulfonylureas and biguanides are still being used for the treatment of diabetes mellitus despite the criticisms raised by the UGDP report [1] and the occasional incurrence of brain damages due to excessive hypoglycemia [2]. Lactic acidosis is also known to be caused by some biguanides [3, 4].

Recent efforts to search for better hypoglycemic agents in our laboratory led to a series of phenethylaminomethylbenzylalcohols,† out of which *l*-α-(3,4-dimethoxyphenethylaminomethyl)-2-hydroxybenzylalcohol 1/2 fumarate [TA-078 (Fig. 1)] was selected for further studies as one of the most effective and least toxic derivatives. TA-078 differs from the conventional hypoglycemic agents, sulfonylureas and biguanides in that its hypoglycemic effects after oral administration are more pronounced in glucose-loaded than fasted animals. It was found that TA-078 stimulates insulin secretion from the pancreas in a more glucose-dependent fashion than tolbutamide.

The present paper describes studies on the hypoglycemic action of TA-078 in some animal species and on its mechanism of action.

MATERIALS AND METHODS

Hypoglycemic agents. TA-078 and its optical isomer were synthesized in the Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd (Saitama, Japan). Tolbutamide and phenformin were purchased from Boehringer Mannheim GmbH (Mannheim, F.R.G.) and Ono Pharmaceutical Co. Ltd (Osaka, Japan), respectively.

For administration, TA-078 and phenformin were dissolved and tolbutamide was suspended in water so as to give the required concns of 10, 5 and 4 ml/kg body wt for the mouse, rat and dog, respectively.

Animals. Male ddY mice (6–8 weeks old) and male Sprague–Dawley rats (6–9 weeks old) were

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† In preparation.

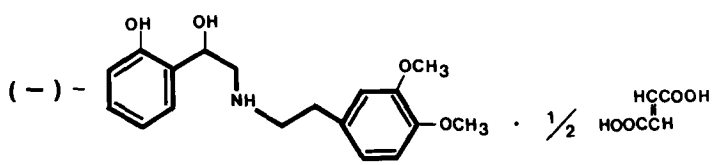

Fig. 1. Chemical structure of TA-078 [*l*-α-(3,4-dimethoxyphenethylaminomethyl)-2-hydroxybenzylalcohol 1/2 fumarate].

purchased from Shizuoka Agricultural Cooperation for Laboratory Animals (Hamamatsu, Shizuoka-ken, Japan). Male beagle dogs were purchased from Yoshiki Farm (Yoshiki, Gifu-ken, Japan). KK mice, which had originally been obtained from the Institute of Medical Science, University of Tokyo (Tokyo, Japan), were inbred to the fifth to eighth generation. Male KK mice which weighed over 30 g body wt at 3–9 months of age and showed increases of more than 40 mg/100 ml in blood glucose 120 min after subcutaneous administration of glucose (1 g/kg) were used.

Diabetic rats were produced by intravenous injection of 60 mg/kg of streptozotocin (Boehringer Mannheim GmbH). Eighteen days after the injection, the average fasting blood glucose level of these rats was about 270 mg/100 ml.

Animal experiments. Mice were fasted for 20 hr, and rats and dogs for 40 hr, prior to experiments unless stated otherwise.

In glucose tolerance tests with mice and rats, glucose (1 g/kg/10 ml for mice, 5 ml for rats) was subcutaneously injected immediately after oral administration of the drug. In glucose tolerance tests with dogs, glucose (1 g/kg) was orally administered along with TA-078 in the drug solution (4 ml/kg).

For estimation of blood glucose alone, blood samples (10 μl) were obtained from the tail tip of mice and rats immediately before and at various time intervals after drug administration.

For determination of immunoreactive insulin (IRI) and immunoreactive glucagon (IRG), blood samples (over 1 ml) were obtained from the femoral vein of mice and the abdominal aorta of rats under ether anesthesia. All blood samples of dogs were taken from the accessory cephalic vein. The blood was mixed with 1/10 vol. of a solution containing EDTA (12 mg/ml) and aprotinin [Trasylol® (50,000 I.U./ml) (Bayer, Leverkusen, F.R.G.)], and centrifuged at 1500 *g* for 10 min to give plasma samples for the insulin and glucagon assays.

Perfusion of isolated rat pancreas. The pancreas was isolated from fasted rats (11–12 weeks old, 320–370 g body wt) and perfused by the procedure of Anderson and Long [5] modified by Grodsky *et al.* [6] at a flow rate of 1.33 ml/min. The basal perfusion medium (pH 7.4) consisted of 117 mM NaCl, 4.7 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 2.5 mM $NaHCO_3$, 1.26 mM $CaCl_2$, 4.5% (w/v) dextran [mean mol. wt 60,000 (Nakarai Chemicals Ltd, Kyoto, Japan)] and 2.8 mM glucose (50 mg/100 ml). The medium was gassed with 95% O_2–5% CO_2 at 37°. The pancreas was perfused first with the basal medium for 20 min in order to stabilize the level of insulin output, then with a test medium containing additional glucose (5.6 mM final concn), a test compound or both for another 20 min, and finally with the basal medium again for 20 min. The effluent was collected at 2-min intervals in tubes containing aprotinin (1000 I.U.) and stored in a refrigerater (−20°) until assayed.

Analytical methods. Glucose was measured enzymatically with glucose oxidase and peroxidase using the kit the 'Blood Sugar-Perid-Test®' (Boehringer Mannheim GmbH). IRI was measured by the double-antibody procedure using the insulin assay kit of 'Insulin Eiken®' (Eiken Immunochemical Laboratory, Tokyo, Japan). Glucagon was immunologically measured using the 30 K antiserum [purchased from the Department of Internal Medicine, University of Texas Southern Medical School (Dallas, TX)] [7].

Statistical significance of difference was determined by Student's *t*-test.

RESULTS

Hypoglycemic effects of TA-078 in mice

In a glucose tolerance test in normal mice, oral administration of TA-078 at a dose of 3 mg/kg and of tolbutamide or phenformin at a dose of 100 mg/kg depressed the blood glucose level by similar extents 60 min after administration (Fig. 2A). The *d*-isomer of TA-078 was without effect (Fig. 2B). The blood glucose concn of fasted mice was lowered by TA-078 at a dose of 30 mg/kg, but only weakly at 3 mg/kg, as shown in Fig. 2C. These hypoglycemic effects were dose-dependent (Fig. 2B and C).

TA-078 was effective in improving the glucose tolerance of KK mice, one of the animal models of diabetes. On the other hand, tolbutamide did not improve it (Fig. 3).

Hypoglycemic effects in rats

Rats seem to be less sensitive to the hypoglycemic action of TA-078. In a glucose tolerance test shown in Fig. 4A, TA-078 caused a significant depression of the blood glucose concn 60 min after administration at an oral dose of 10 mg/kg. The depression by 30 mg/kg TA-078 was approximately equal to that of 30 mg/kg tolbutamide 60 min after administration. Interestingly TA-078 did not lower the blood glucose concn below the initial normal level even at a dose of 100 mg/kg, while tolbutamide at the dose of 30 mg/kg eventually produced a hypoglycemia which lasted for a few hours (Fig. 4A). Particularly noteworthy was the lack of hypoglycemic effects when TA-078 was administered to normal fasted rats (Fig. 4B). Under the same conditions, 30 mg/kg tolbutamide depressed the fasting blood glucose concn by more than 30%.

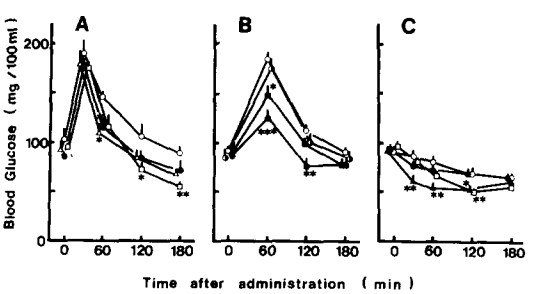

Fig. 2. Effects of TA-078 on glucose tolerance (A and B) and fasting blood glucose levels (C) in mice. TA-078 [1 (■), 3 (●) and 30 (▲) mg/kg], *d*-isomer of TA-078 [100 mg/kg (◑)], tolbutamide [100 mg/kg (□)] and phenformin [100 mg/kg (△)] were orally administered to groups of four to six fasted mice immediately before a subcutaneous load of glucose (1 g/kg). Points and bars represent the means and S.E. Significant difference from control (○): $^*P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

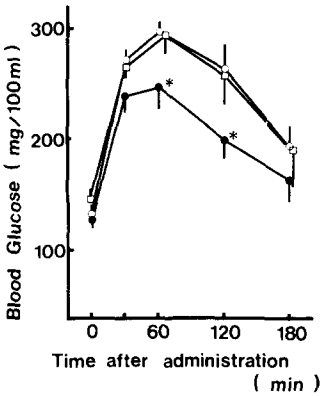

Fig. 3. Effects of TA-078 (a racemic form) and tolbutamide on glucose tolerance in KK mice. Racemic TA-078 [10 mg/kg (●)] and tolbutamide [100 mg/kg (□)] were orally administered to groups of 9–10 fasted male KK mice immediately before a subcutaneous load of glucose (1 g/kg). Points and bars represent the means and S.E. Significant difference from control (○): *P < 0.05.

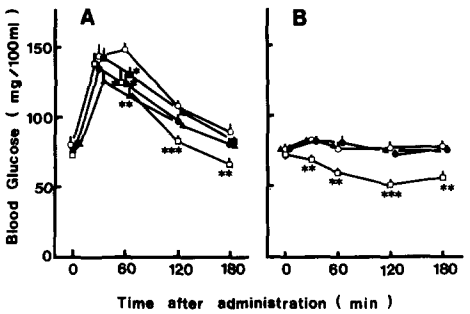

Fig. 4. Effects of TA-078 and tolbutamide on glucose tolerance (A) and fasting blood glucose levels (B) in rats. TA-078 [10 (■), 30 (●) and 100 (▲) mg/kg] and tolbutamide [30 mg/kg (□)] were orally administered to groups of five fasted rats immediately before a subcutaneous load of glucose (1 g/kg). Points and bars represent the means and S.E. Significant difference from control (○): *P < 0.05, **P < 0.01 and ***P < 0.001.

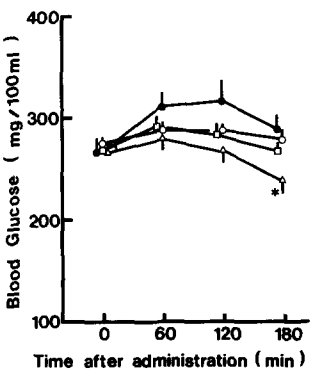

Fig. 5. Effects of hypoglycemic agents on glucose tolerance in streptozotocin-diabetic rats. TA-078 (●), tolbutamide (□) and phenformin (△) at a dose of 100 mg/kg were orally administered immediately before a subcutaneous load of glucose (1 g/kg) to groups of six streptozotocin-diabetic rats fasted for 20 hr. Points and bars represent the means and S.E. Significant difference from control (○): *P < 0.05.

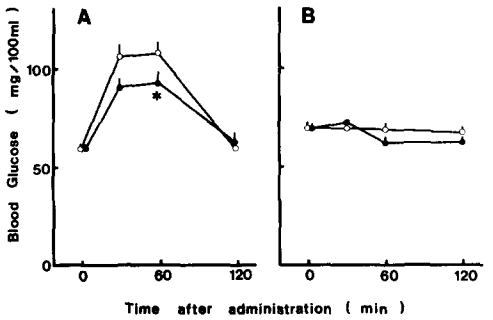

Fig. 6. Effects of TA-078 on glucose tolerance (A) and fasting blood glucose levels (B) in beagle dogs. TA-078 (●) at a dose of 2.5 (A) or 5 (B) mg/kg was orally administered to fasted beagle dogs in aqueous solution (4 ml/kg) along with (A) or without (B) glucose (1 g/kg). Points and bars represent the means of 12 (A) or 6 (B) animals and S.E. Significant difference from control (○): *P < 0.05.

When TA-078 (100 mg/kg) or tolbutamide (100 mg/kg) was orally administered to streptozotocin-diabetic rats, neither improved the glucose tolerance (Fig. 5). On the other hand, phenformin (100 mg/kg) lowered the blood glucose concn 180 min after administration (Fig. 5).

Hypoglycemic effects in beagle dogs

Glucose tolerance tests in beagle dogs revealed that about half of the animals showed relatively poor glucose tolerance as represented by elevated glucose tolerance curves, i.e. increases the blood glucose concn by over 40 mg/100 ml 30 or 60 min after glucose loading (1 g/kg). It is in these animals that TA-078 at an oral dose of 2.5 mg/kg exerts its hypoglycemic effect (Fig. 6A). Thus, their sensitivity to the hypoglycemic action of TA-078 was nearly as high as in mice, but unlike in mice (Fig. 7) the fasting blood glucose concn of these dogs was not significantly depressed by 5 mg/kg TA-078 (Fig. 6B). In a separate experiment with four fasted dogs an oral dose of 50 mg/kg TA-078 did not lower the initial blood glucose level (77.0 ± 1.1 mg/100 ml) when determined 1 hr (79.0 ± 3.8 mg/100 ml) and 2 hr (73.8 ± 5.8 mg/100 ml) after administration. In those animals which tolerated the glucose load and showed lower glucose tolerance curves, the effect of TA-078 was only marginal (data not shown).

Effects of TA-078 on plasma insulin and glucagon levels in mice

It has been established that the principal mechanism of the hypoglycemic action of sulfonylurea antidiabetics is stimulation of insulin secretion from the pancreas. In order to find out the mechanism for the hypoglycemic action of TA-078, its effects on plasma insulin and glucagon levels were examined.

Oral administration of TA-078 (3 mg/kg) alone to normal fasted mice resulted in a two-fold increase in plasma IRI at 15 and 30 min, which was probably responsible for a sustained hypoglycemia in the TA-078-treated mice (Fig. 7A and B). Glucose loading alone also induced a moderate rise in plasma IRI, although the difference from the control was statistically insignificant in the particular experiment

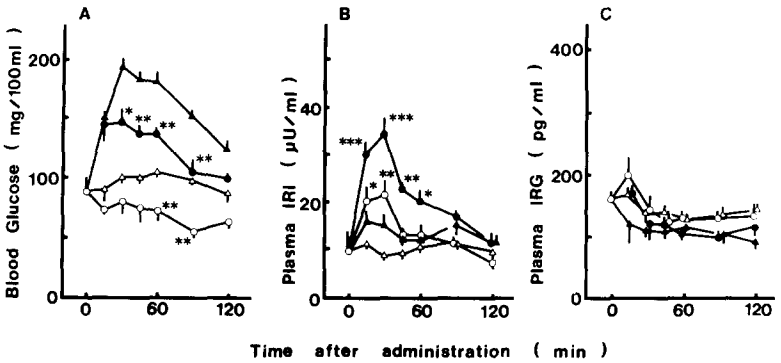

Fig. 7. Effects of TA-078 on blood glucose (A), plasma IRI (B) and IRG (C) levels in fasted mice. Glucose (1 g/kg, closed symbols) or saline (open symbols) was subcutaneously injected immediately after oral administration of TA-078 (circle) at a dose of 3 mg/kg or distilled water (triangle). Groups of five mice were killed at each time. Points and bars represent the means and S.E. Significant difference from the respective control groups: $^{*}P < 0.05$ and $^{**}P < 0.01$.

shown in Fig. 7B. This glucose-induced rise in plasma IRI was further augmented by simultaneous administration of TA-078 with a resultant depression of the glucose tolerance curve (Fig. 7A and B). Plasma IRG levels were not significantly affected by the administration of TA-078, but the average IRG levels of the TA-078-treated groups were above those of the respective control groups in the early phase (at 15 min) after drug administration (Fig. 7C).

Effects of TA-078 and tolbutamide on plasma insulin and glucagon levels in rats

TA-078 also dose-dependently elevated the level of plasma IRI in glucose-loaded rats, but it had no significant effect on the IRI level in fasted animals determined 30 min after oral administration of the drug (Fig. 8). TA-078 did not influence the level of plasma IRG in both glucose-loaded and fasted animals. In contrast to TA-078, tolbutamide (100 mg/kg) elevated the levels of plasma IRI in both animal groups, and it significantly decreased the level of plasma IRG in fasted rats (Fig. 8).

The time courses of plasma IRI and IRG levels were followed after administration of 100 mg/kg TA-078 in fasted rats. This high dose of TA-078 caused only a slight lowering of blood glucose, which was significant at 30 and 120 min but not comparable to the overt hypoglycemia produced by the same dose of tolbutamide (Fig. 9C). Nevertheless, TA-078 did cause a rapid rise followed by a sudden decrease in plasma IRI (Fig. 9A). On the other hand, tolbutamide produced a somewhat less prompt but more sustained elevation in plasma IRI which lasted for a full hour (Fig. 9A). Of particular interest was the concurrent sharp drop in plasma IRG in tolbutamide-treated rats, while the TA-078 treatment caused no significant change except for an increase at 120 min (Fig. 9B). The dissimilarity in

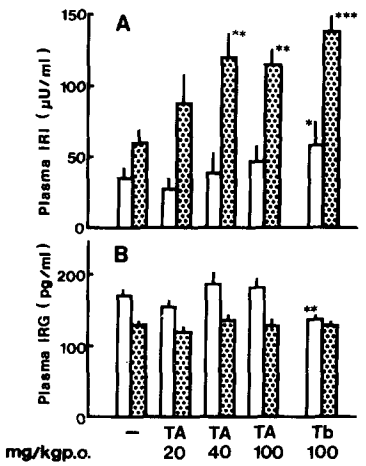

Fig. 8. Effects of TA-078 and tolbutamide on plasma IRI (A) and IRG (B) levels in fasted rats. Oral administration of TA-078 (TA) or tolbutamide (Tb) was immediately followed by subcutaneous injection of 1 g/kg glucose (dotted column) or saline (open column). All rats were killed 30 min after drug administration. Each bar represents the S.E.M. of five animals. Significant difference from the respective controls: $^{*}P < 0.06$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

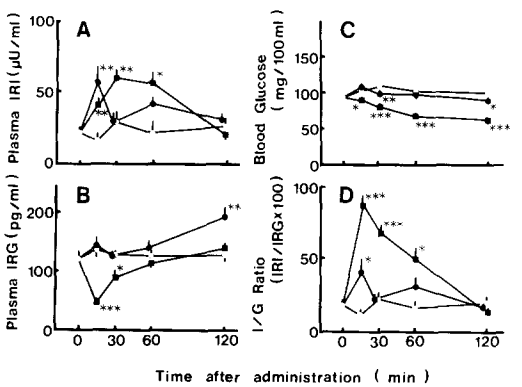

Fig. 9. Effects of TA-078 and tolbutamide on plasma IRI (A) and IRG (B) and blood glucose (C) levels in fasted rats. TA-078 (●) and tolbutamide (■) were orally administered at a dose of 100 mg/kg. The IRI to IRG ratio [IRI/IRG ratio (D)] was calculated for each animal. Groups of six rats were killed at each time. Points and bars represent the means and S.E. of six animals. Significant difference from control (□): $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

the effects on the plasma levels of the two hormones between TA-078 and tolbutamide becomes more conspicuous if the ratio of plasma IRI to IRG in individual rats is plotted on the graph (Fig. 9D). Tolbutamide gave high ratios at 15, 30 and 60 min, while the ratio with TA-078 was significantly higher than the control only at 15 min, but even this ratio was much lower compared to the tolbutamide group.

Effects of perfusion of TA-078 and tolbutamide on the secretion of insulin from the isolated rat pancreas

If TA-078 elevates the plasma IRI level by acting directly on the pancreas, perfusion of the rat pancreas with TA-078 should result in an elevated output of insulin in the perfusate. When the rat pancreas was perfused with the basal medium containing 2.8 mM glucose (50 mg/100 ml), basal insulin secretion was kept depressed (Fig. 10A). Addition of 10 μg/ml TA-078 to this perfusion medium did not stimulate insulin secretion significantly (Fig. 10B). In contrast, addition of the same concn of tolbutamide resulted in an immediate and marked increase in insulin output (Fig. 10D). This insulin output, however, returned nearly to the basal level within 6 min, and thereafter it was followed by a small second peak. When the concn of TA-078 was increased to 50 μg/ml, insulin secretion was stimulated (Fig. 10C). After reaching the peak, the insulin level gradually returned to the basal level without producing a second peak.

An increase in the glucose concn in the perfusion medium to 5.6 mM (100 mg/100 ml) brought about an instant and transient rise in insulin secretion (Fig. 10A). When TA-078 (10 μg/ml) was present in this high-glucose medium, a sharp peak of stimulated insulin secretion appeared shortly after the initiation of perfusion with TA-078 and it was followed by an elevated plateau till the end of the perfusion with TA-078 (Fig. 10B). On addition of 10 μg/ml tolbutamide to the high-glucose medium, insulin release showed a sharp primary peak similar to the one observed at the low glucose concn, but the following second peak was far greater than the one with low glucose (Fig. 10D). An increase in the concn of TA-078 in the high-glucose medium to 50 μg/ml resulted in a marked stimulation of insulin secretion with apparently two peaks of comparable sizes (Fig. 10D).

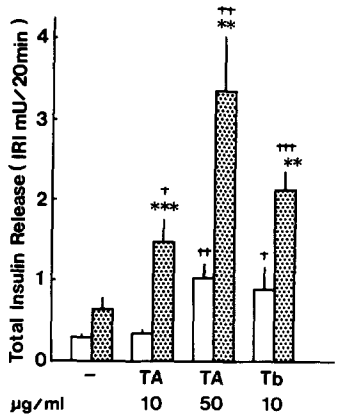

Fig. 11. Effects of TA-078 (TA) and tolbutamide (Tb) on insulin release from perfused rat pancreas. The total amounts of insulin released from perfused rat pancreas during the test period of 20 min were calculated from the data of the experiments shown in Fig. 10. Open and dotted columns represent the amount of insulin released in the presence of 2.8 and 5.6 mM glucose, respectively. Bars represent S.E.M. Significant difference from the respective controls (no drug): †$P < 0.05$, ††$P < 0.01$ and †††$P < 0.001$. Significant difference between insulin amounts at the low and high glucose concns: **$P < 0.01$ and ***$P < 0.001$.

The total amounts of insulin secreted during the drug infusion are shown in Fig. 11. As was expected from Fig. 10, the addition of 10 μg/ml TA-078 to the low-glucose medium had no effect on the amount of insulin output, while the addition of the same concn of tolbutamide increased it more than two-fold.

The increase in the glucose concn of the basal medium to 5.6 mM produced a two-fold stimulation of insulin secretion. The stimulation ratio did not change in the presence of 10 μg/ml tolbutamide, but it was markedly augmented by the presence of either 10 or 50 μg/ml TA-078 along with high glucose.

DISCUSSION

TA-078 represents a new class of orally active hypoglycemic agents, new not only in its chemical structure but also in its mode of action. Its hypo-

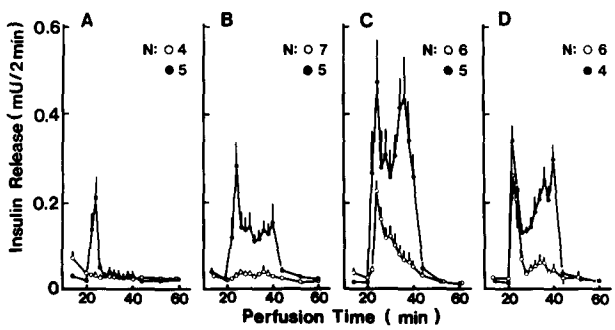

Fig. 10. Effects of TA-078 and tolbutamide on insulin release from perfused rat pancreas. TA-078 [10 μg/ml (B) and 50 μg/ml (C)], tolbutamide [10 μg/ml (D)]or no drug (A) was perfused in the presence of 2.8 (○) or 5.6 mM (●) glucose. Points and bars represent the means and S.E.

glycemic activity, unlike sulfonylureas and biguanides [8], is much more pronounced in glucose-loaded animals than in fasted animals (Figs 2, 4 and 6). Thus, the fasting blood glucose levels in rats and dogs resist the hypoglycemic action of TA-078 at doses 10 times higher than the minimal dose required to improve glucose tolerance. This unique hypoglycemic property is probably reflected in its efficacy in improving glucose tolerance in KK mice vs the inefficacy of tolbutamide (Fig. 3) on one hand and in its inefficacy in streptozotocin-diabetic rats vs the efficacy of phenformin (Fig. 5) on the other. Since the pancreas of KK mouse is known to be functioning, albeit with some deviation from normal [9, 10], while that of streptozotocin-diabetic rats are devoid of intact B-cells in the islets of Langerhans [11–13], the hypoglycemic action of TA-078 probably requires functioning B-cells like tolbutamide but its action probably involves aspects different from the tolbutamide action.

The possibility that TA-078 may act by stimulation of insulin secretion from the pancreas was indicated by the increase in plasma IRI concomitant to the lowering of blood glucose in mice (Fig. 7) and directly confirmed in the perfusion experiments with rat pancreas (Figs 10 and 11).

The perfusion experiments demonstrated that the threshold concn for the stimulation of insulin secretion in the presence of 2.8 mM glucose was higher for TA-078 than for tolbutamide and that the rate of stimulation of insulin secretion on increasing the glucose concn to 5.6 mM was augmented by TA-078, but not by tolbutamide (Fig. 11). These results may explain the differences in the mode of action between TA-078 and tolbutamide, i.e. the weaker hypoglycemic activity in fasted animals (Figs 4 and 9) and the more potent activity of TA-078 in glucose-loaded normal (Fig. 2A) and KK (Fig. 3) mice than those of tolbutamide.

However, the difference in relative glucose dependency of the insulin release stimulation by these drugs is not likely to be the sole explanation for the contrasting effects of these drugs on fasting blood glucose, because TA-078, which is capable of stimulating insulin release *in vivo* in fasted animals (Fig. 9A) and *in vitro* at a low glucose concn (Fig. 10C) when given at a high dose or high concn, is still unable to produce hypoglycemia in fasted rats treated with the excessive dose of TA-078 (Figs 4B and 9C).

The plasma insulin to glucagon ratio rather than their absolute concns is considered important in regulating the blood glucose concn [14], and glucagon is known to be the principal counter-hypoglycemic hormone for insulin-induced hypoglycemia [15, 16]. Therefore, the time course of changes in both plasma IRI and IRG after TA-078 or tolbutamide administration was investigated in fasted rats (Fig. 9). Tolbutamide unequivocally increased plasma IRI over an extended period, but the rise of plasma IRI after TA-078 administration was only transient, disappearing within 30 min (Fig. 9A). This may mean that the amount of secreted insulin may be a critical factor to induce hypoglycemia. On the other hand, plasma IRG was sharply and significantly decreased in the early phase after the administration of tolbutamide, while almost no effect was observed in the same period after TA-078 administration (Fig. 9B). This difference, presented in a more conspicuous way in the graph of the IRI to IRG ratios (Fig. 9D), may be a more likely explanation for the hypoglycemia produced by tolbutamide on one hand and for the stationary blood glucose level in TA-078-treated fasted rats on the other.

The reduction of plasma IRG levels by tolbutamide has been observed in man and ducks by Samols *et al.* [17]. This may be ascribable to an inhibition of glucagon secretion by stimulated insulin release [18], but the fact that a maximal lowering of glucagon secretion by tolbutamide occurred before its maximal stimulation of insulin secretion (Fig. 9A and B) suggests that tolbutamide directly inhibited glucagon secretion. The finding that TA-078 showed no effects on plasma IRG levels at the early stage despite its stimulation of insulin secretion (Fig. 9) may indicate the possibility that TA-078 directly stimulates glucagon secretion or it in some way counteracts the inhibitory action of insulin. The significant elevation of rat plasma IRG 120 min after administration of TA-078 (Fig. 9B) suggests the former possibility.

The chemical structure of TA-078 reminds one of catecholamines and some β-adrenergic agents. Adrenergic mechanisms have been known to participate in the regulation of blood glucose levels by various mechanisms. β-Adrenergic agents stimulate both insulin [19, 20] and glucagon [21, 22] release from the pancreas, and inhibit glucose uptake by muscle [23–25]. In fact, isoproterenol and other β-adrenergic agents are known to elevate fasting blood glucose in rats [26, 27] (and our unpublished observations). TA-078 differs from the β-adrenergic agents in its lack of the hyperglycemic effect in fasted animals (Figs 2C, 4B, 6B, 7A, and 9C). The possibility that TA-078 may act as an agonist with a high specificity towards the β-receptors of the B (and A) cells of the pancreas and as an antagonist towards the β-receptors of muscle remains to be investigated. A β-antagonist, ICI 66082, which lowers blood glucose by direct stimulation of both insulin secretion and peripheral glucose uptake has been reported [28].

In conclusion, TA-078 is a new, orally active hypoglycemic agent structurally unrelated to the known antidiabetic drugs. Its hypoglycemic action is more pronounced in glucose-loaded than fasted animals probably owing to its stimulatory effects on insulin release being dependent on high plasma glucose levels. This property may prove to be a useful characteristic when it is used as an antidiabetic agent.

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