Inhibition of Insulin Release from Rat Pancreatic Islets by Drugs that Are Analogues of Dopamine

STEPHEN P. ARNERIĆ, SAMSON A. CHOW, JOHN P. LONG, AND LAWRENCE J. FISCHER

SUMMARY

Various synthetic dopamine (DA) analogues have been shown to produce glucose intolerance and inhibit the compensatory increase in serum insulin during an oral glucose tolerance test (OGTT). To investigate the possibility that there is a direct action of dopamine analogues to inhibit glucose-stimulated insulin release from the endocrine pancreas, the following compounds were compared with the effects of epinephrine (EPI) on isolated rat pancreatic islets: apomorphine (APO), pergolide, lergotrile, TL-99 (2-dimethylamino-6,7-dihydroxytetralin), and RDS-127 (2-di-*n*-propylamino-4,7-dimethoxyindane). EPI, TL-99, and pergolide inhibited insulin release in a concentration-dependent fashion (10^{-7}–10^{-5} M), whereas lergotrile inhibited at 10^{-5} M but not at 10^{-6} M. RDS-127 and APO were ineffective at 10^{-5} M, but produced a greater than 50% inhibition at 2×10^{-4} M. The potencies of the DA analogues fell into two groups: compounds that are approximately as active as EPI (e.g., TL-99 and pergolide) or compounds that are relatively inactive (e.g., APO, lergotrile, and RDS-127). The inhibitory actions of EPI, TL-99, and pergolide were blocked by the α_2-adrenergic receptor antagonist yohimbine, whereas the DA receptor antagonist, sulpiride, had no effect, suggesting an action initiated at α_2-adrenergic receptors. Drugs from both groups produced marked glucose intolerance and inhibited the compensatory increase in insulin during an OGTT. Adrenodemedullation blocked the glucose intolerance and inhibition of insulin release caused by RDS-127, whereas these effects of TL-99 were not attenuated. These data, obtained in vitro and in vivo, show that selective dopamine agonists, such as RDS-127, reduce glucose-stimulated insulin release indirectly through adrenal medullary secretions, whereas the effect of less selective agonists, such as TL-99, directly inhibit the release of insulin from the endocrine pancreas. DIABETES 1984; 33:888–93.

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Drugs that are analogues of dopamine (DA) produce hyperglycemia and alter serum insulin concentrations in humans and in laboratory animals.[1–5] The metabolic effects of dopaminergic agents should be of clinical interest, since these compounds are gaining widespread therapeutic application in the treatment of a variety of disease states,[6,7] including Parkinson's disease,[8] neuroendocrine disorders,[9] cardiovascular disturbances,[10,11] and obesity.[12] Despite the reports of altered glucose homeostasis and the growing therapeutic application of DA analogues, the mechanisms by which these agents alter endocrine pancreas function are not well established.

DA and synthetic DA analogues are capable of eliciting pharmacologic effects by binding to α-adrenergic receptors and/or dopaminergic receptors, depending on the biologic system under investigation.[13–15] Activation of α-adrenergic receptors in pancreatic islets produces an inhibition of glucose-stimulated insulin release,[16] and DA itself reduces glucose-stimulated release by this mechanism.[17] The hyperglycemia caused by DA administration, therefore, can be at least partially due to a direct inhibition of insulin secretion.[3]

Compared with DA itself, many of the newer experimentally and therapeutically useful DA analogues have much less α-adrenergic receptor agonist actions. In rats, DA receptors in pancreatic islets do not play a direct role in modulating insulin release from β-cells,[17] and it follows that the newer analogues of DA, having less α-adrenergic agonist properties, would be less likely to directly inhibit insulin release and produce hyperglycemia. Apomorphine, the prototypical DA receptor agonist, and RDS-127 (2-di-*n*-propylamino-4,7-dimethoxyindane), a novel experimental DA receptor agonist, are examples of DA analogues that have relatively few α-adrenergic properties.[18] In contrast, TL-99 (2-dimethylamino-6,7-dihydroxytetralin) is a DA analogue that has nearly equal potency to activate α-adrenergic or DA receptors.[14] Unexpectedly, all three DA analogues were recently shown to produce hyperglycemia, glucose intolerance, and inhibition of the compensatory increase in serum insulin meas-

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ured during an oral glucose tolerance test (OGTT) in rats.[1,19] It is possible that TL-99, by interacting with α-adrenergic receptors in pancreatic islets, could cause these effects through an inhibition of insulin release from the pancreas. On the other hand, there is evidence that the hyperglycemic effects of apomorphine and RDS-127 result from sympathoadrenal activation, permitting an epinephrine-induced increase in blood glucose.[1,19] It remains possible, however, that the effects of apomorphine and RDS-127 are, at least in part, the result of a direct inhibition of insulin release from pancreatic islets.

The potencies with which various DA analogues directly inhibit glucose-stimulated insulin release in isolated pancreatic islets have not been previously determined. Those analogues that produce hyperglycemia by a direct action on the endocrine pancreas would be expected to have a potency for inhibiting insulin release from isolated pancreatic islets similar to that of epinephrine. Analogues producing hyperglycemia by acting on DA receptors in the central nervous system should be less potent in their action to inhibit hormone release from isolated islets. In the present study, we determined the relative potencies of various DA analogues and epinephrine for inhibition of glucose-stimulated insulin release from rat pancreatic islets. See Figure 1 for the chemical structures of the DA analogues used in this study. The possible involvement of dopaminergic and/or adrenergic receptors in the potent inhibition of in vitro insulin release by certain DA analogues was assessed using the antagonists sulpiride and yohimbine. In addition, we examined whether the adrenal medulla is required for the in vivo inhibition of insulin release caused by the administration of RDS-127 and TL-99, these compounds being representative of relatively specific and nonspecific dopamine agonists, respectively. The results in this report provide additional evidence that DA-like drugs can produce hyperglycemia by two different mechanisms.

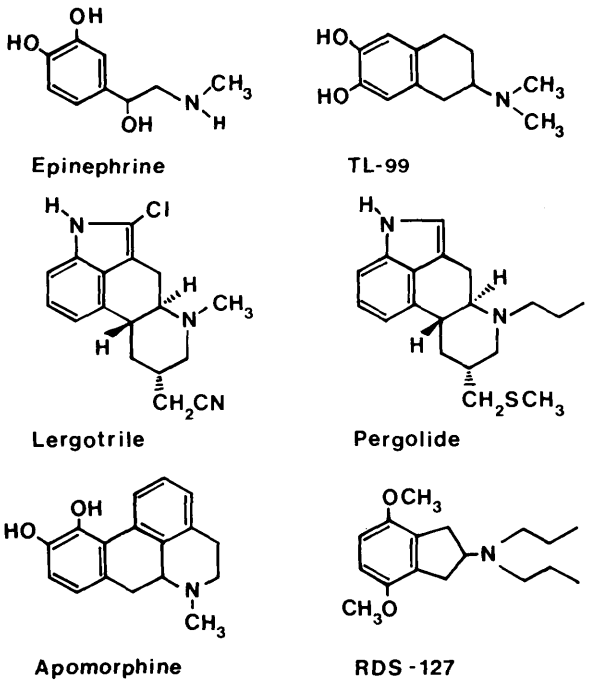

FIGURE 1. The chemical structures of the compounds that were tested for their ability to inhibit glucose-stimulated insulin release from isolated pancreatic islets.

MATERIALS AND METHODS

Animals. Male, Sprague-Dawley rats (200–350 g) were subjected to a 12 h/12 h light/dark schedule with the lights on from 0730 h to 1930 h. Standard rat chow and water were available ad libitum. Room temperature was 21 ± 2°C.

Isolated islets. Islets of Langerhans were isolated by collagenase digestion of the pancreas as described by Lacy and Kostianovsky.[20] Groups of 10 islets collected in 0.1-ml volume were added to 13 × 100-mm, siliconized glass tubes. Krebs-Ringer bicarbonate buffer (0.8 ml) containing 2.0 mg/ml bovine serum albumin and low glucose (0.75 mg/ml) was added to all tubes so that a final volume of 1.0 ml contained 0.6 mg/ml glucose. Dopamine receptor agonists (2.4×10^{-4}–10^{-7} M) or receptor antagonists (10^{-5}–10^{-8} M) were added in a total volume of 0.1 ml to obtain the final concentrations as indicated; control tubes received 0.1 ml vehicle (0.9% NaCl). Dopamine receptor agonists were added to the islets and incubated at 37°C for 10 min before high glucose stimulation. Antagonists (or vehicle), when used, were added to islets 5 min before addition of the agonists. After this pretreatment schedule, the tubes were gently centrifuged to pellet the islets and the supernatant was aspirated and discarded. Test compounds (i.e., antagonists and/or agonists) were added back to the tubes in 0.9 ml buffer solution that contained high glucose (3.0 mg/ml). Trasylol (500 KIU/ml; FBA Pharmaceuticals, Inc., New York, New York) was introduced into all tubes to inhibit proteolytic degradation of insulin. The tubes were flushed with 95% O_2/5% CO_2 and capped. After gentle shaking in a water bath at 37°C for 45 min, the tubes were removed and the islets pelleted by gentle centrifugation. The supernatant was obtained and frozen (−20°C) until assay for immunoreactive insulin (IRI). Included in each experiment were two groups of control islets that were not treated with antagonists or agonists, but were exposed only to 0.6 mg/ml glucose (low-glucose control) or 3.0 mg/ml glucose (high-glucose control) for 45 min. These control islets were handled in exactly the same manner as islets that were treated with antagonists and agonists, except that additions of vehicle were made instead of solutions containing drugs. Data were calculated as ng IRI/islet/45 min incubation. Because of the usual day-to-day variation in glucose-stimulated insulin release from isolated pancreatic islets, the data are expressed as percent of high-glucose controls to facilitate the statistical comparison of drug effects.

OGTTs. Rats were fasted for 18 ± 1 h before these experiments, with water still available ad libitum. For repetitive withdrawal of blood samples, a catheter was placed in the jugular vein the afternoon before experimentation (1400–1800 h). One end of the catheter (0.3-mm i.d. silastic tubing) was inserted through the right jugular vein into the atrium of the heart of rats anesthetized with pentobarbital sodium (40 mg/kg, i.p.), while the other end was exteriorized behind the head. Catheters were flushed with heparin (100 U/ml) to maintain patency. Blood samples were obtained from conscious, unrestrained animals.

Adrenodemedullation was completed under pentobarbital sodium anesthesia (40 mg/kg, i.p.) through a midline abdominal laporatomy performed 1 wk before experimentation.

Saline (vehicle control), TL-99 (3.6 μmol/kg), or RDS-127

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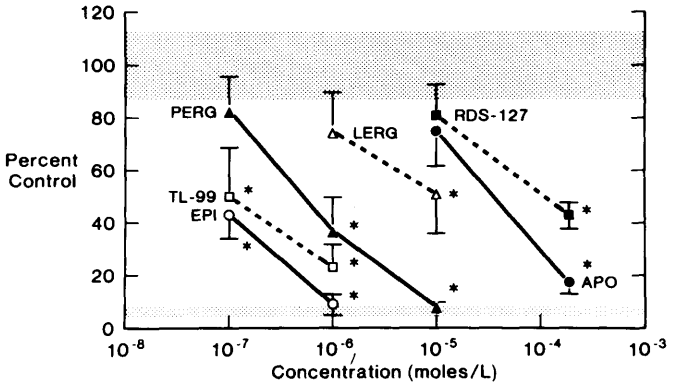

FIGURE 2. The concentration-response relationships for inhibition of glucose-stimulated release of insulin from isolated rat islets by epinephrine and various DA analogues. Values are expressed as a percent of the high-glucose-vehicle control response. Each point represents the mean ± SEM of 3–5 experiments. The saline (vehicle control) responses are indicated by the shaded regions (mean ± SEM), in which the upper region is for high-glucose control (18.1 ± 2.3 ng; IRI/islet/45 min) and the lower region is for low-glucose control (1.1 ± 0.3 ng IRI/islet/45 min). The values for the control responses are pooled from all the experiments that were performed (N = 22). An asterisk (*) indicates that the value is statistically different from the corresponding high-glucose control, P < 0.05.

(6.4 μmol/kg) was administered subcutaneously 30 min before the OGTT. D-Glucose (3.0 g/kg, given as a 30% solution) was introduced into the stomach by intubation. Consecutive blood samples (0.5 ml) were withdrawn just before DA receptor agonist or saline administration (−30 min); immediately before D-glucose administration (0 min); and 30, 90, and 150 min after oral glucose. Normal saline (0.5 ml) was immediately given after each collection to replace the blood volume removed. Serum glucose concentration was analyzed by a Beckman II Glucose Analyzer (Beckman Instruments, Fullerton, California), and insulin concentration was determined by the radioimmunologic method described below.

Insulin assay. Immunoreactive insulin (IRI) was measured radioimmunologically by the method of Morgan and Lazarow.[21] Rat insulin (Novo, Copenhagen) was used as the standard and guinea pig antiserum to porcine insulin (Dr. P. Wright) was the antibody source. ^{125}I-insulin was prepared by the Diabetes Research Center Core Unit at the University of Iowa. Radiochemical purity of ^{125}I-insulin was verified by a high-performance liquid chromatographic technique.[22]

Statistics. Data were analyzed by one-way analysis of variance using Duncan's new multiple-range test to detect treatment differences.[23] Data expressed as percent of control were transformed to the corresponding log values before statistical analysis. The 0.05 level of probability was chosen as the criterion of statistical significance. Values indicated in the text or figures represent the mean ± SEM

Drugs. RDS-127 (2-di-*n*-propylamino-4,7-dimethoxyindane hydrochloride) was synthesized in the Medicinal Chemistry Department at the University of Iowa by Dr. J. Mott. The synthesis and structural verification of RDS-127 has been reported previously.[24] Apomorphine hydrochloride was purchased from Sigma Chemical Company (St. Louis, Missouri). The following compounds were obtained as generous gifts from the indicated companies: TL-99 (2-di-methylamino-6,7-dihydroxytetralin hydrochloride), Merck, Sharp and Dohme (West Point, Pennsylvania); lergotrile mesylate and pergolide mesylate, Eli Lilly and Company (Indianapolis, Indiana); sulpiride injectable, Delegrange Laboratories (Paris, France); and yohimbine hydrochloride, K and K Laboratories, Inc. (Plainview, New York).

RESULTS

Pancreatic islets. Figure 2 shows the concentration-response relationship of epinephrine and various DA analogues to inhibit in vitro glucose-stimulated insulin release. Epinephrine and TL-99 inhibited insulin release >50% at concentrations of 10^{-7} and 10^{-6} M. At a concentration of 10^{-6} M, epinephrine and TL-99 had profound effects on insulin release, the effects of pergolide were significantly less than those of epinephrine, and lergotrile had no significant inhibitory effects. At 10^{-5} M, pergolide had a maximal inhibitory effect, lergotrile also significantly inhibited release, but both APO and RDS-127 were inactive. The inhibitory effects of APO and RDS-127 were not detected until very high concentrations (2×10^{-4} M) were used.

Figure 3 shows the effects of the antagonists yohimbine (10^{-5} M) and sulpiride (10^{-8} M) on the inhibitory effects of 10^{-6} M concentrations of epinephrine, TL-99, or pergolide. The α_2-adrenergic receptor antagonist, yohimbine, blocked the inhibitory effects of epinephrine, TL-99, and pergolide, whereas the DA receptor antagonist, sulpiride, had no effect. The antagonists alone, yohimbine (10^{-5} M) or sulpiride (10^{-8} M), had no significant effect on insulin release stimulated by high glucose (97 ± 5% and 101 ± 4% of control, respectively, N = 3). The antagonists were not used with APO or RDS-127 due to the low potency of these agonists for inhibition of glucose-stimulated insulin release from pancreatic islets.

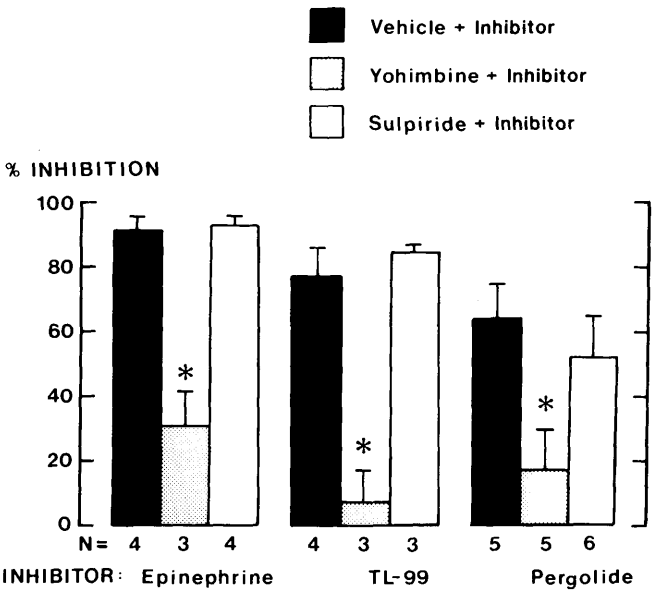

FIGURE 3. The effect of pretreatment with vehicle, yohimbine (10^{-5} M), or sulpiride (10^{-8} M) on the inhibitory effects of epinephrine, TL-99, and pergolide (all at 10^{-6} M). Values are expressed as percent inhibition of the insulin release obtained from the high-glucose-vehicle control. Each bar represents the mean ± SEM response of the number of experiments indicated by N. An asterisk (*) indicates that the value is statistically different from the inhibitory response, obtained using no antagonist pretreatment, P < 0.05.

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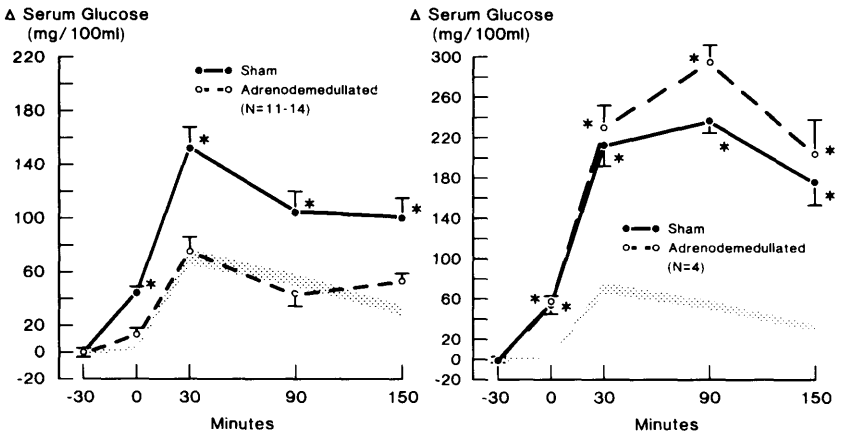

FIGURE 4. The effects of sham operation or adrenodemedullation on the glucose intolerance produced by RDS-127 (left panel) and TL-99 (right panel) during an OGTT. RDS-127 (6.4 μmol/kg), TL-99 (3.6 μmol/kg), or saline was administered subcutaneously immediately after the −30 min blood sample. Values represent the change in serum glucose from the pre-experiment (−30 min) value. The basal glucose concentrations (−30 min) for the sham and adrenodemedullated animals were 89 ± 3 (N = 23) and 87 ± 2 mg/dl (N = 26), respectively. The shaded region represents the mean ± SEM (N = 19–20) of the saline (vehicle control) responses. An asterisk (*) indicates that the value is statistically different from the vehicle control response, P < 0.05.

OGTT. To demonstrate whether RDS-127 and TL-99 exerted direct or indirect actions to alter β-cell function in vivo, the effects of adrenodemedullation on the ability of these dopamine analogues to inhibit insulin release during an OGTT were determined. If the inhibitory actions of RDS-127 or TL-99 were attenuated by adrenodemedullation, then adrenal medullary secretions could be implicated in contributing to the ability of these drugs to impair β-cell function.

There were no differences between sham-operated or adrenodemedullated animals in serum glucose or serum insulin concentrations during an OGTT. Therefore, the serum glucose and insulin responses for saline-treated (vehicle control) animals were pooled from sham-operated and adrenodemedullated animals; these control values are shown in Figures 4 and 5. Adrenodemedullation blocked the glucose intolerance produced by RDS-127 (Figure 4, left panel), whereas adrenodemedullation did not attenuate the glucose intolerance produced by TL-99 (Figure 4, right panel). Adrenodemedullation significantly attenuated the inhibition by RDS-127 of the compensatory increase in serum insulin caused by glucose administration (Figure 5, left panel), whereas the inhibitory effects of TL-99 on glucose tolerance were not affected (Figure 5, right panel). Figure 6 shows the effect of adrenodemedullation on the changes in the insulin/glucose ratio produced by RDS-127 or TL-99 30 min after an oral glucose load, the insulin/glucose ratio being an index of β-cell function. Both RDS-127 and TL-99 significantly inhibited the normal response of the β-cells to an oral glucose load. While adrenodemedullation prevented the effects of RDS-127, adrenodemedullation had no effect on the inhibitory actions of TL-99.

DISCUSSION

The present study shows that there are wide differences in the potencies required for dopamine analogues to inhibit glucose-stimulated insulin release from rat pancreatic islets. Pergolide and TL-99 have potencies for inhibition of glucose-stimulated insulin release similar to epinephrine, while RDS-127 and apomorphine are much less potent when tested in the pancreatic islet system. Previously, it has been shown that all of these drugs will produce hyperglycemia after doses that produce similar central dopaminergic stimulant effects. Based on potency to inhibit insulin secretion from pancreatic islets, the results suggest that TL-99 and pergolide could produce alterations in blood glucose by directly altering insulin secretion in an epinephrine-like manner, whereas apomorphine and RDS-127 may lack sufficient potency for a direct action in pancreatic islets.

It is clear from the data obtained from OGTTs that the effects of RDS-127 and TL-99 to produce abnormal glucose tolerance and inhibit in vivo insulin release are brought about by different mechanisms. The presence of the adrenal medulla is necessary for the inhibitory action of RDS-127 on pancreatic function during an OGTT, but not for the effect

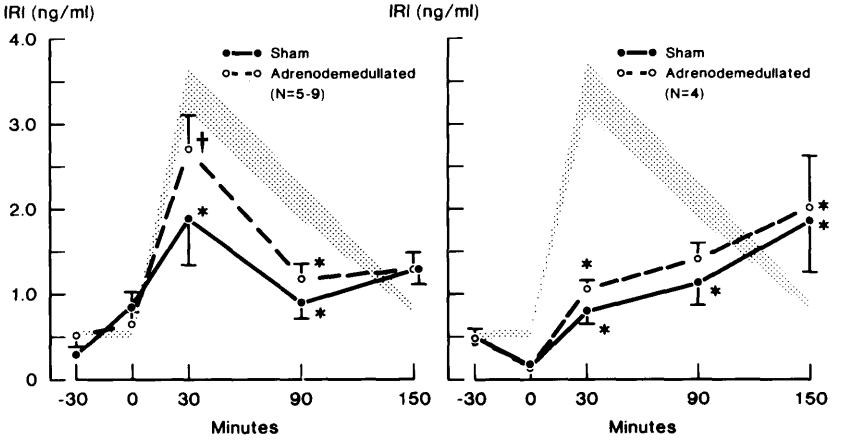

FIGURE 5. The effects of sham operation or adrenodemedullation on the inhibition caused by RDS-127 (left panel) or TL-99 (right panel) of the compensatory increase in serum insulin during an OGTT. RDS-127 and TL-99 were administered as described in the legend to Figure 4. Values represent the mean ± SEM response of the number of experiments indicated by N. The shaded region represents the mean ± SEM of the saline (vehicle control) responses (N = 4). An asterisk (*) indicates that the value is statistically different from the vehicle control response, P < 0.05. A dagger (†) indicates that the value is statistically different from the sham-operated animals, P < 0.05.

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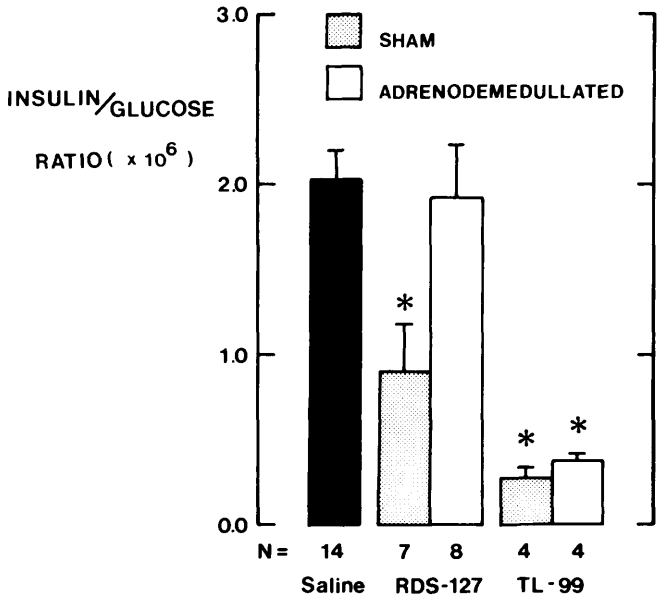

FIGURE 6. The effects of sham operation or adrenodemedullation on the changes in the insulin/glucose ratio produced by RDS-127 or TL-99, 30 min after an oral glucose load. RDS-127 and TL-99 were administered as described in the legend to Figure 4. Values represent the mean ± SEM response of the number of experiments indicated by N. An asterisk (*) indicates that the value is statistically different from the vehicle control (saline) response, $P < 0.05$.

of TL-99. Previously, it has been shown that the adrenal gland is required for the action of RDS-127, apomorphine,[1] and lergotrile[25] to produce hyperglycemia in unchallenged rats. Together with the results presented here, it appears that RDS-127, lergotrile, and apomorphine alter β-cell function in vivo through adrenal medullary secretions, but that TL-99 acts as a direct inhibitor of insulin release. Although the effects of pergolide have not been fully evaluated in vivo, its high potency to inhibit insulin release in vitro suggests that its action in vivo could be a direct one (i.e., similar to that of TL-99).

Previous work suggests that DA reduces insulin release in vitro through α-adrenergic and not through DA receptor-mediated processes. Itoh and co-workers[17] demonstrated that phentolamine, an α-adrenergic receptor antagonist, blocks the inhibitory action of DA, whereas high concentrations of the DA receptor antagonists haloperidol and pimozide (5 μM) were ineffective. Recently, Nakaki and co-workers[16] have suggested that α-receptors of the α_2-adrenergic subtype are present in pancreatic islets, since yohimbine (10^{-5} M) was shown to completely block the inhibitory action of the α-adrenergic receptor agonist epinephrine. In the present report, yohimbine (10^{-5} M) was also shown to attenuate the inhibitory effects of epinephrine, TL-99, and pergolide (all at 10^{-6} M). In contrast, the DA receptor antagonist sulpiride, which is a very weak antagonist of α-adrenergic and serotonin receptors,[26] had no effect on the inhibitory actions of these three agents. The dose of sulpiride used here (10^{-8} M) has been established to block DA receptor-mediated actions in vitro.[27] Therefore, our results, obtained using synthetic DA analogues of diverse chemical structures, support the results obtained with DA by Itoh and co-workers. Although the structural requirements that allow a DA analogue to directly modify β-cell function are not apparent (refer to Figure 1), it is clear that a catecholamine component is not required (e.g., pergolide). These conclusions are different from those derived by Feldman and co-workers,[28] who found that phenylethylamine derivatives require hydroxyl groups on the aromatic ring to have a significant action to inhibit glucose-stimulated insulin release in vitro. Further work will be necessary to completely elucidate the structural requirements for adrenergic receptor-mediated inhibition of insulin release.

The apparent differences in the mechanism of the hyperglycemic effects of the dopamine analogues studied here are consistent with differences among these drugs observed in other biologic test systems. Apomorphine, RDS-127, and lergotrile have been well characterized and are considered to be relatively specific for interacting with dopamine receptors in the CNS.[18,29,30] These dopamine analogues appear to have much less central α- and β-adrenergic receptor agonist action than does dopamine itself. The ability of TL-99 and the inability of RDS-127 to interact with α_2-adrenergic receptors within peripheral tissues other than the pancreas has been well documented.[13,15,31,32] Pergolide is known to interact with peripheral α-adrenergic receptors.[11] Thus, in considering the hyperglycemic action of dopamine analogues, it is consistent with results obtained in other biologic systems to suggest that analogues of DA, such as TL-99, act to directly inhibit insulin release in pancreatic islets through α_2-adrenergic receptors, whereas RDS-127, apomorphine, and, probably, lergotrile activate the sympathoadrenal system through an initial action at dopamine receptors in the CNS.[19,25]

Central activation of epinephrine release from the adrenal is a well-characterized system for producing hyperglycemia.[33-35] Circulating epinephrine acts to inhibit insulin release and through stimulation of glucagon release to facilitate hepatic gluconeogenic and glyconeolytic mechanisms.[4,5,36] All of these actions of epinephrine allow the accumulation of serum glucose. Since RDS-127 and apomorphine have been shown to increase the release of epinephrine from the adrenal medulla when given in doses sufficient to produce hyperglycemia,[37,38] this catecholamine is probably the mediator through which these compounds reduce glucose-stimulated insulin release and produce hyperglycemia. Epinephrine inhibits glucose-stimulated insulin release through α_2-adrenergic receptor mechanisms[16] and is probably an important physiologic modulator of insulin release.[35,39,40] An epinephrine-mediated hyperglycemic effect caused by apomorphine and RDS-127 is also supported by previous evidence showing that the α-adrenergic receptor antagonist phentolamine will block the glucose intolerance and inhibition of glucose-stimulated insulin release caused by the administration of these drugs.[1] Evidence indicating that apomorphine and RDS-127 act at central dopaminergic receptors is available and includes antagonism by central administration of a dopamine receptor antagonist and the fact that the drugs have higher potencies for producing hyperglycemia when administered into the cerebral ventricles of rats.[19]

In summary, two mechanisms can account for the ability of the DA analogues studied here to inhibit glucose-stimulated insulin release in vivo. Apomorphine and RDS-127,

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lacking potency to inhibit insulin secretion in vitro, act in vivo by activating central dopaminergic receptors, which results in the release of epinephrine from the adrenal medulla.[37] In contrast to this indirect mechanism, TL-99 and, probably, pergolide, through α-adrenergic actions, directly inhibit glucose-stimulated insulin release by interacting at receptors located in pancreatic islets.

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REFERENCES

[1] Arnerić, S. P., Chow, S. A., Long, J. P., and Fischer, L. J.: Dopamine receptor agonist-induced hyperglycemia in rats: involvement of the adrenal medulla and the endocrine pancreas. In press. J. Pharmacol. Exp. Ther. 1983.

[2] George, D. T., and Rayfield, E. J.: L-Dopa induced plasma glucagon release. J. Clin. Endocrinol. Metab. 1974; 39:618–21.

[3] Håkanson, R., Lundquist, I., and Rerup, C.: On the hyperglycemic effect of dopa and dopamine. Eur. J. Pharmacol. 1967; 1:114–19.

[4] Leblanc, H., Lachelin, G. C. L., Abu-Fadil, S., and Yen, S. S. C.: The effect of dopamine infusion on insulin and glucagon secretion in man. J. Clin. Endocrinol. Metab. 1977; 44:196–98.

[5] Rayfield, E. J., George, D. T., Eichner, H. L., and Hsu, T. H.: L-Dopa stimulation of glucagon secretion in man. N. Engl. J. Med. 1975; 293:589–91.

[6] Bianchine, J. R., Shaw, G. M., Greenwald, J. E., and Dandalides, S. M.: Clinical aspects of dopamine agonists and antagonists. Fed. Proc. 1978; 37:2434–39.

[7] Corsini, G. U., and Gessa, G. L., Eds.: Apomorphine and Other Dopaminomimetics, Vol. 2, Clinical Pharmacology. New York, Raven Press, 1981.

[8] Schmidt, M. J.: The pharmacotherapy of Parkinson's disease. *In* Neuropharmacology of Central Nervous System and Behaviorial Disorders. Palmer, G. C., Ed. New York, Academic Press, 1981:150–71.

[9] Müller, E. E., Parrerai, A. E., Cocchi, D., and Mantegazza, P.: Endocrine profile of ergot alkaloids. Life Sci. 1977; 21:1545–58.

[10] Goldberg, L. I.: Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol. Rev. 1972; 24:1–29.

[11] Lokhandwala, M. F., and Barrett, R. J.: Cardiovascular dopamine receptors: physiological, pharmacological and therapeutic implications. J. Autonomic Pharmacol. 1982; 3:189–215.

[12] Zigmond, M. J., Heffner, T. G., and Stricker, E. M.: The effect of altered dopaminergic activity on food intake in the rat: evidence for an optimal level of dopaminergic activity for behavior. Prog. Neuropsychopharmacol. 1980; 4:351–62.

[13] Timmermans, P. B. M. W. M., and Van Zwieten, P. A.: The postsynaptic α_2-adrenoreceptor. J. Auton. Pharmacol. 1981; 1:171–83.

[14] Welch, J. J., Kim, H. S., Braunwalder, A., Stone, G., Loo, P., and Liebman, J. M.: Effects of dopamine autoreceptor agonists at α_2-adrenoreceptors. Abstract. Soc. Neurosci. 1982; 8 (Suppl. 1):128.24.

[15] Maixner, W., Flynn, J. R., Arnerić, S. P., Koons, J. C., Cannon, J. G., and Long, J. P.: II. Pharmacological studies with derivatives of 2-aminotetralin, benzo[f]quinoline, benzo[g]quinoline, apomorphine and clonidine suggest a pharmacological dissimilarity between peripheral presynaptic dopamine and alpha receptors. J. Pharmacol. Exp. Ther. 1983; 224 (Suppl. 2):352–58.

[16] Nakaki, T., Nakadate, T., and Kato, R.: α_2-Adrenoreceptors modulating insulin from isolated pancreatic islets. Naunyn Schmiedebergs Arch. Pharmacol. 1980; 313:151–53.

[17] Itoh, M., Furman, B. L., and Gerich, J. E.: Dopaminergic suppression of pancreatic somatostatin secretion. Acta Endocrinol. (Copenh.) 1982; 101:56–61.

[18] Arnerić, S. P., Long, J. P., Williams, M., Goodale, D. B., Mott, J., Lakoski, J. M., and Gebhart, G. F.: RDS-127 (2-di-*n*-propylamino-4,7-dimethoxyindane): central effects of a new dopamine receptor agonist. J. Pharmacol. Exp. Ther. 1983; 224:161–70.

[19] Arnerić, S. P., Chow, S. A., Bhatnagar, R. K., Webb, R. L., Fischer, L. J., and Long, J. P.: Evidence that central dopamine receptors modulate sympathetic neuronal activity to the adrenal medulla to alter glucoregulatory mechanisms. Neuropharmacology 1984; 23:137–47.

[20] Lacy, P. E., and Kostianovsky, M.: Method for the isolation of intact islets of Langerhans from the rat pancreas. Diabetes 1967; 16:35–39.

[21] Morgan, C. R., and Lazarow, A.: Immunoassay of insulin: two-antibody system. Diabetes 1963; 12:115–25.

[22] Fischer, L. J., Thies, R. L., and Charkowski, D.: High performance liquid chromatographic separation of insulin, glucagon, and somatostatin. Anal. Chem. 1978; 50:2143–44.

[23] Steele, R. G. D., and Torrie, J. H.: Principles and Procedures of Statistics. New York, McGraw-Hill, 1960:106–14.

[24] Sindelar, R. D., Mott, J., Barfknecht, C. F., Arnerić, S. P., Flynn, J. R., Long, J. P., and Bhatnagar, R. K.: 2-Amino-4,7-dimethoxyindane derivatives: synthesis and assessment of dopaminergic and cardiovascular actions. J. Med. Chem. 1982; 25:858–64.

[25] Schmidt, M. J.: Dopamine agonist-induced hyperglycemia in rats: effects of lergotrile mesylate. Eur. J. Pharmacol. 1979; 59:95–101.

[26] Kohli, J. D., and Cripe, L. D.: Sulpiride, a weak antagonist of norepinephrine and 5-hydroxytryptamine. Eur. J. Pharmacol. 1979; 56:283–86.

[27] Koons, J. C., Flynn, J. R., and Long, J. P.: Antagonist properties of phentolamine at both presynaptic alpha 2-adrenoceptors and presynaptic dopamine receptors using field stimulated right cat atria. Eur. J. Pharmacol. 1983; 88:311–17.

[28] Feldman, J. M., Boyd, A. E., and Lebovitz, H. E.: Structural determinants of catecholamine action on *in vitro* insulin release. J. Pharmacol. Exp. Ther. 1971; 176:611–21.

[29] Martin, G. E., Williams, M., and Haubrich, D. R.: A pharmacological comparison of 6,7-dihydroxy-2-dimethylaminotetralin (TL-99) and N-*n*-propyl-3-(3-hydroxyphenyl) piperidine (3-PPP) with selected dopamine agonists. J. Pharmacol. Exp. Ther. 1982; 223 (Suppl. 2):298–304.

[30] Seeman, P.: Brain dopamine receptors. Pharmacol. Rev. 1980; 32:229–313.

[31] Maixner, W., Arnerić, S. P., Abou Zeit-Har, M. S., Lecompte, J., Verimer, T., Cannon, J. G., Lee, T., and Long, J. P.: Pharmacological effects of 2-aminotetralins, octahydrobenzo[f]quinolines, and clonidine on the isolated guinea pig ileum. Eur. J. Pharmacol. 1981; 71:483–88.

[32] Arnerić, S. P., Maixner, W., Long, J. P., Mott, J., Barfknecht, C. F., Perez, J. A., and Cannon, J. G.: Structure activity relationships of 2-aminotetralin and 2-aminoindanes: inhibitory neuroeffector mechanisms in isolated guinea pig ilea. Arch. Int. Pharmacodyn. Ther. 1982; 258:84–99.

[33] Himms-Hagen, J.: Sympathetic regulation of metabolism. Pharmacol. Rev. 1967; 19:367–461.

[34] Niijima, A.: Control of liver function and neuroendocrine control of blood glucose levels. *In* Integrative Function of the Autonomic Nervous System. Brooks, C., Koizumi, K., and Sato, A., Eds. Tokyo, Elsevier/North-Holland Biomedical Press, 1979:68–83.

[35] Smith, P. H., Woods, S. C., and Porte, D., Jr.: Control of the endocrine pancreas by the autonomic nervous system and related neural factors. *In* Integrative Function of the Autonomic Nervous System. Brooks, C., Koizumi, K., and Sato, A., Eds. Tokyo, Elsevier/North-Holland Biomedical Press, 1979:84–97.

[36] Yajima, M., and Ui, M.: Gluconeogenesis in epinephrine-induced hyperglycemia. Am. J. Physiol. 1974; 227:1–8.

[37] Arnerić, S. P., Chow, S. A., Webb, R. L., Bhatnagar, R. K., Fischer, L. J., and Long, J. P.: Evidence for central pathways mediating the hyperglycemia produced by dopamine receptor agonists in the rat. Soc. Neurosci. 1982; 8:421.

[38] Quik, M., and Sourkes, T. M.: Regulation of adrenal tyrosine hydroxylase activity: neuronal versus local control studied with apomorphine. Biochem. Pharmacol. 1976; 25:1157–66.

[39] Ahren, B., Ericson, L. E., Lindquist, I., Loren, I., and Sindler, F.: Adrenergic innervation of pancreatic islets and modulation of insulin secretion by the sympatho-adrenal system. Cell Tissue Res. 1981; 216:15–30.

[40] Lebovitz, H. E., and Feldman, J. M.: Pancreatic biogenic amines and insulin secretion in health and disease. Fed. Proc. 1973; 32:1797–1802.

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