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Impairment of Albuterol-Induced Suppression of Food Intake in Diabetes Mellitus

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BITAR, M. S., A. F. KEIS, S. E. OWUSU, R. MULVEN AND E. B. DESOUZA. *Impairment of albuterol-induced suppression of food intake in diabetes mellitus.* PHARMACOL BIOCHEM BEHAV **41**(3) 483–487, 1992. – Albuterol (salbutamol), a β_2 adrenoreceptor agonist, produced a dose-dependent decrease in food intake in Sprague-Dawley male control rats. This phenomenon appeared to be impaired in streptozotocin (STZ) diabetic rats. The density of β_2 adrenoreceptors in the ventromedial hypothalamic nucleus was increased as a function of diabetes. In contrast, a decrease in the ventromedial hypothalamic 5-hydroxyindoleacetic acid (5-HIAA) concentration, an indicator of serotonin (5-hydroxytryptamine; 5-HT) release or turnover rate, was observed in this disease state. Neither the β_2 adrenoreceptor level nor 5-HT turnover rate was altered in the periventricular hypothalamic nucleus of STZ diabetic rats. The concentrations of 5-HT in both hypothalamic nuclei were unchanged in these animals. Neurochemical and behavioral abnormalities featured in the diabetic state were reversed with institution of insulin therapy. These data conclude that diabetes-related impairment in the anorexic action of albuterol may be due to derangements in ventromedial hypothalamic β_2 adrenoreceptor function.

Diabetes Ingestive behavior β_2 adrenoreceptors Albuterol

NEUROCHEMICAL, hormonal, and behavioral abnormalities have been reported to occur in experimental and clinical diabetes. In this context, brain monoamine turnover rate (1-3,20,37), sexual behavior (12), and serum concentrations of luteinizing hormone and testosterone (1,16,32) are generally decreased in diabetes mellitus. In contrast, feeding (4,19) and paradoxical sleep (10) are increased in this disease state.

A number of studies indicated that brain serotonin (5-HT) is involved in the regulation of food intake (28). Intrahypothalamic injection of 5-HT (13,21,22) and the administration of drugs that release, for example, fenfluramine, or inhibit synaptic reuptake, for example, fluoxetine, of 5-HT have been reported to reduce food intake in rodents (14,30,31,38). In addition, the β_2 adrenergic agonist albuterol is also anorexic (5), an action that appears to be mediated, at least in part, by the ability of this agonist to enhance 5-HT turnover within the CNS (15,27,35). Indeed, pretreatment with propranolol, a beta adrenoreceptor antagonist, abolished albuterol or 5-HT-related decreased food intake (5,21). Contrastingly, overeating and weight gain occurred in rats following 5-HT depletion (6). These findings, together with the paucity of information concerning derangements of transmitter-ingestive behavior interaction in diabetes, prompted us to examine the relationships between hypothalamic 5-HT turnover rate, β_2 adrenoreceptor density, and ingestive behavior in streptozotocin (STZ)-treated rats, an animal model for type I diabetes mellitus.

METHOD

Animals

Adult male Sprague-Dawley rats (Charles River Breeding Laboratories) weighing 225 g at the beginning of the experiment were used in this study. Rats were housed individually and maintained and tested in their home cages in a temperature-controlled colony (21–24°C) with a 12L:12D cycle.

Treatment

Diabetes was induced by an IV injection of streptozotocin (STZ; 65 mg/kg body wt.) diluted in 0.05 M sodium citrate, pH 4.5; control rats received buffer alone by the same route. Diabetic animals were randomly subdivided into two groups,

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with one group receiving no antidiabetic treatment while the other received subcutaneous injection of crystalline zinc insulin and lente insulin (1 : 1 ratio) 5–8 U daily starting 7 days after STZ injection and continuing for 20–25 days. The dose of insulin was determined on the basis of the daily urine and weekly blood tests for glucose. The animals were given ad lib access to tapwater and ground Purina rat chow. Chow was offered in glass feeding cups with spill-resistant lids for 7 days. Following this initial 7-day acclimation period, the duration of daily food access was reduced from 24 h to a daily 4 h period. Fresh food and water were supplied daily between 10:00–10:30 a.m. Rats were adapted to the maintenance conditions described above and to daily injections of 0.9% NaCl (1.0 ml/kg body wt., IP) between 9:45–10:00 a.m. for at least 2 weeks before experiments.

Food Intake

The effect of albuterol sulfate (salbutamol) on feeding during the first hour of the dark phase of the lighting cycle was examined after 20 h of food deprivation. Albuterol sulfate or its vehicle (saline) were injected IP 15 min prior to onset of the feeding session. Each animal was tested only once. A treatment group received either 0.0, 2.5, 5, 10, or 20 mg/kg albuterol. The injection volume utilized throughout all experiments was 1.0 ml/kg body weight. Food consumption was recorded at 60 min following session onset. In experiments in which pretreatment with *d*,L-propranolol hydrochloride or phentolamine (5 mg/kg, IP) was used, albuterol was administered at a dose of 5 mg/kg, IP.

Labeling of β_2 Adrenoreceptors in Slide-Mounted Brain Sections

For consistency, the feeding test procedure was followed, except rats were not injected with albuterol. Animals were sacrificed by decapitation between 9:00–10:30 a.m. and trunk blood was collected for the determination of serum glucose concentration. Brains were removed, frozen in powdered dry ice, and sectioned in the coronal plane (10 μm). Tissue sections were thaw mounted onto chrome alum/gelatin-subbed microscope slides and stored at −70°C until assayed.

β_2 adrenoreceptor subtypes were labeled using previously described conditions (11,29). Briefly, slide-mounted brain sections were brought to room temperature and incubated in 20 mM Tris-HCl/15 mN NaCl buffer, pH 7.4, containing 100–150 pM ^{125}I-cyanopindolol (^{125}ICYP-specific activity 2200 Ci/mmol; Dupont New England Nuclear, Boston, MA) and various competing drugs for 70 min at room temperature. ^{125}ICYP binding to β_2 adrenoreceptors was defined as ^{125}ICYP binding in the presence of 70 nM of the β_1 selective antagonist ICI-89, 406 minus the nonspecific binding. Nonspecific binding was defined as binding in the presence of 100 μM of the nonselective beta agonist isoproterenol. After incubation, tissue sections were washed in buffer at 4°C for three consecutive 20-min periods, dipped in a deionized water-rinse, and dried rapidly under a stream of cold, dry air. The kinetic analysis and pharmacological specificity of ^{125}ICYP binding have been described previously (11).

Autoradiography

The dry, labeled, slide-mounted sections were apposed to ^{3}H-Ultrofilm (LKB, Gaithersburgh, MD) and after 24–48 h of exposure the autoradiograms were developed and the tissues were stained with toluidine blue.

Analysis of autoradiographic data. In autoradiograms prepared with ^{3}H-Ultrofilm, optical density readings, construction of standard curves, and rapid quantification of data were carried out with a Loats PC-based computerized image analysis system (Amersham/Searle Corporation, Des Plaines, IL). The film optical density was related to the molar concentration of radioactivity using ^{125}I-labeled brain mash standards generated and analyzed concomitantly with the autoradiograms. We utilized a power function to describe the relationship between optical density and radioactivity inasmuch as the Loats image analysis system indicated a best fit for the power function as opposed to a linear or log function.

Serotonin Metabolism

Tissues from hypothalamic nuclei were homogenized in 100 μl perchloric acid containing 3×10^{-8}M *N*-methylserotonin as an internal standard. 5-HT and 5-hydroxyindolacetic acid (5-HIAA) were determined using liquid chromatography with electrochemical detection (3). The chromatographic separation of 5-HT and 5-HIAA was achieved using a C18 reverse-phase column of 5 μm particle size, 8 mm inside diameter, and 10 cm length. The mobile phase consisted of 8 ml acetonitrile, 7.2 ml triethylamine, 1.53 g heptane sulfonic acid, and 0.1 g sodium EDTA per liter of deionized water. The final pH was adjusted to 2.53 with 85% phosphoric acid. A model 600 Waters pump was used to deliver the solvent at a rate of 1.3 ml/min. The model LC-4BAS amperometric detector with a glassy carbon electrode was used at an oxidation potential of +0.55 V. Twenty-μl aliquots of the acidified supernatant were injected into the system. The results were recorded with a dual-channel LKB recorder.

Statistical Analysis

Statistical differences between treatment groups were assessed using analysis of variance (ANOVA) and Duncan's multiple-range test. The level of significance was chosen as $p < 0.05$.

RESULTS

Experiment 1

The anorexic action of albuterol in normal and diabetic rats is shown in Table 1. Albuterol-induced anorexia was assessed at 20–25 days following STZ injection. When injected with saline, both normal and STZ-treated rats ate substantial amounts of food following 20-h deprivation. Albuterol induced a dose-dependent decrease in food intake in normal rats. It is noteworthy, however, that these doses of albuterol caused only a slight reduction in feeding in STZ-diabetic animals.

Experiment 2

Since the results of Experiment 1 suggested a decreased sensitivity to the anorectic effects of albuterol in STZ rats, in Experiment 2 we examine whether this phenomenon (resistance to albuterol anorexic action) was due to lack of insulin. The preceding experiment was repeated with the addition of a group of diabetic animals given replacement therapy with insulin. Two to 3 weeks following insulin therapy, the anorectic action of albuterol was examined as described in Experiment 1. Ingestive behavior was studied following IP injection of 0.9% NaCl or albuterol sulfate. Table 1 clearly shows that the ability of albuterol to suppress food intake was similar in normal and insulin-treated diabetic animals.

TABLE 1

EFFECT OF ALBUTEROL ON FOOD INTAKE OF CONTROL, DIABETIC, AND INSULIN-TREATED DIABETIC RATS

Treatment	Dose (mg/kg)	1 h Food Intake (g/rat)		
		Control	Diabetic	Diabetic & Insulin
Saline	0.0	8.34 ± 0.40	8.54 ± 0.36	8.74 ± 0.38
Albuterol	1.25	5.65 ± 0.48*	7.67 ± 0.60	5.32 ± 0.32*
Albuterol	2.50	2.89 ± 0.35*	7.30 ± 0.56	3.10 ± 0.30*
Albuterol	5.00	2.46 ± 0.18*	7.02 ± 0.31	2.25 ± 0.28*
Albuterol	10.00	1.82 ± 0.11*	7.95 ± 0.28	1.73 ± 0.33*
Albuterol	20.00	1.65 ± 0.21*	7.78 ± 0.47	1.62 ± 0.26*

Values represent the means ± SEM for at least 30 animals.
*Significant at $p < 0.05$ from saline-injected group.

Experiment 3

This study was conducted to investigate whether diabetes-induced resistance to the anorectic action of albuterol was due to a reduction in the number of β_2 adrenoreceptors. ^{125}ICYP binding to β_2 adrenoreceptors was increased as a function of diabetes in ventromedial but not periventricular hypothalamic nucleus (Table 2). Insulin treatment reversed the increase in ventromedial hypothalamic β_2 adrenoreceptors. Since the concentrations of ^{125}ICYP used in the present study (100–150 M) result in a high functional occupancy of β_2 adrenoreceptors (70–80%), it would be reasonable to speculate that the increased ^{125}ICYP binding to β_2 adrenoreceptors observed in STZ-diabetic rats reflected primarily an alteration in the density of binding sites. However, possible alterations in the affinity of receptors in diabetes cannot be ruled out.

Experiment 4

This study demonstrates the effect of the diabetic state on 5-HT metabolism in ventromedial and periventricular hypothalamic nuclei. In Table 3, the 5-HT concentrations in both hypothalamic nuclei were not altered as a function of diabetes. However, the level of its metabolite 5-HIAA was significantly decreased in the ventromedial but not the periventricular hypothalamic nucleus. A normalization of 5-HIAA levels in the ventromedial hypothalamic nucleus of STZ-diabetic rats was achieved by the daily administration of insulin.

TABLE 2

EFFECTS OF STZ AND INSULIN TREATMENT ON β_2 ADRENORECEPTORS' DENSITIES IN SELECTED HYPOTHALAMIC NUCLEI

Treatment	β_2 Adrenoreceptors	
	VMN	PVN
Control	13.2 ± 1.3	16.5 ± 2.9
Diabetic	21.8 ± 2.0*	15.2 ± 2.0
Diabetic and Insulin	14.8 ± 2.4	18.2 ± 2.3

Values are expressed as fmol per mg of protein and represent the means ± SEM for at least 12 animals. VMN, ventromedial hypothalamic nucleus; PVN, paraventricular nucleus.
*Significant at $p < 0.05$ from vehicle-injected rats.

Experiment 5

This study was designed to investigate whether the anorectic action of albuterol could be prevented by the IP injection of 5 mg/kg propranolol or phentolamine. Propranolol abolished the ability of albuterol to inhibit food intake in control animals. This phenomenon was not seen with the alpha adrenoreceptor antagonist phentolamine (Table 4).

DISCUSSION

The present study documents that albuterol, a β_2-adrenergic agonist (7–9), produces a dose-dependent decrease in food intake in control rats. This phenomenon appears to be impaired in STZ-diabetic rats. The density of β_2 adrenoreceptors in the ventromedial hypothalamic nucleus was increased as a function of diabetes. In contrast, a decrease in the ventromedial hypothalamic 5-HT turnover rate was observed in this disease state. Neither β_2 adrenoreceptor levels nor 5-HT turnover rate were altered in the periventricular hypothalamic nucleus of STZ diabetic rats. Our results concerning albuterol-induced suppression of food intake are consistent with previous reports (5,23); however, the relationship between albuterol and diabetes represents a novel finding.

The above behavioral and neurochemical abnormalities are not likely to be due to a direct toxic effect of STZ because the dose employed acts selectively on beta cells (17,18). The most compelling evidence, however, was that insulin treatment normalized the aberration in beta adrenoreceptor density, 5-HT turnover rate, and the inability of albuterol to suppress food intake.

Diabetes-induced resistance to the anorectic action of albuterol is not unique to this drug since similar results have been reported with amphetamine (24) and tricyclic antidepressants (25). Therefore, the impaired response may be a common feature of the hyperglycemic condition and not a drug-specific phenomenon.

Several lines of evidence have indicated that monoaminergic neurons at the level of the ventromedial hypothalamic nucleus and periventricular nucleus are involved in the regulation of ingestive behavior. In this regard, direct administration of adrenoreceptor agonists including epinephrine, isoproteronol, albuterol, and terbutaline into the hypothalamus of freely moving rats resulted in a marked suppression of food intake (23). The hypothalamic adrenoreceptor sites that inhibited feeding were reported to have characteristics expected of clas-

TABLE 3

EFFECTS OF STZ AND INSULIN TREATMENT ON 5-HT METABOLISM IN VARIOUS HYPOTHALAMIC NUCLEI

Treatment	Compound (pmol/mg protein)	VMN	PVN
Control	5-HT	38.6 ± 2.2	28.4 ± 2.4
	5-HIAA	26.4 ± 1.8	17.6 ± 1.6
Diabetic	5-HT	36.8 ± 3.4	30.6 ± 2.8
	5-HIAA	16.3 ± 1.4*	20.3 ± 3.0
Diabetic and Insulin	5-HT	43.8 ± 4.1	32.5 ± 3.7
	5-HIAA	28.7 ± 3.0	19.3 ± 2.8

Values represent the means ± SEM for at least seven animals. VMN, ventromedial hypothalamic nucleus; PVN, paraventricular nucleus; 5-HT, serotonin; 5-HIAA, 5-hydroxy-indolacetic acid.

*Significant at $p < 0.05$ from control group.

sical β_2 adrenoreceptors (23). These adrenoreceptors appear to be associated with and produce their effects through a catecholamine-sensitive adenylate cyclase (23). In view of the above published reports, it is reasonable to speculate that diabetes-induced resistance to the anorectic action of albuterol noted in the present study is a reflection of a decrease in the number of β_2 adrenoreceptors and/or a biochemical impairment in the processes involved in the generation of cyclic AMP. The former possibility is unlikely because an increase rather than a decrease in the number of β_2 adrenoreceptors was observed in the STZ-diabetic rats. This novel finding supports the premise that a dissociation between adrenoreceptor density and agonist efficacy exists in diabetes. Alternatively, the possibility that the diminished responsiveness of diabetic animals to albuterol is due to altered accumulation of the drug in blood plasma or brain cannot be excluded.

The observed decrease in ventromedial hypothalamic concentrations of 5-HIAA in diabetes is indicative of reduced rate of turnover of 5-HT in this disease state. This is probable because changes in the levels of 5-HIAA that occur in response to various pharmacological and physiological conditions have been related to an altered 5-HT turnover (36). Moreover, a high correlation exists between indices of brain 5-HT turnover and activity of serotonergic neurons (26,33). These data provide an additional explanation consistent with the concept that the impairment in the anorectic action of albuterol in diabetes is due, at least in part, to the hypoactivity of brain serotonergic mechanism. A case in point is the previous findings that albuterol potentiates the behavioral response to 5-hydroxytryptophan, a precursor of 5-HT (27), and that propranolol inhibits the reduction of food intake caused by intrahypothalamic injection of 5-HT (21).

Brain β_2 adrenoreceptors are regulated inversely by changes in serotonergic neuronal activity (34). Thus, the increase in ventromedial hypothalamic β_2 adrenoreceptors densities might be a manifestation of a functional deficit in serotonergic neurons. Indeed, our data showing that the rate of release or turnover of 5-HT (Table 3) is diminished during diabetes gives credence to this hypothesis.

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TABLE 4

EFFECTS OF VARIOUS PHARMACOLOGICAL TREATMENTS ON ALBUTEROL-RELATED SUPPRESSION OF FOOD INTAKE IN CONTROL AND STZ-DIABETIC RATS

		1 h Food Intake (g/rat)			
		Control		Diabetic	
Treatment	Dose (mg/kg)	Saline	Albuterol	Saline	Albuterol
Vehicle	0	7.20 ± 0.4	3.50 ± 0.30*	8.12 ± 0.52	7.82 ± 0.45
Phentolamine	5	6.80 ± 0.3	3.10 ± 0.28*	7.30 ± 0.47	7.53 ± 0.62
Propranolol	5	8.30 ± 0.5	7.70 ± 0.42	7.78 ± 0.58	6.87 ± 0.48

Phentolamine and propranolol were respectively injected 60 and 30 min prior to albuterol. Albuterol (5 mg/kg) was injected 15 min before rats had access to food.

Values represent the means ± SEM for at least 15 animals.

*Significant at $p < 0.05$ from saline-injected control animals.

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