Neurotensin Hyperglycemia: Evidence for Histamine Mediation and the Assessment of a Possible Physiologic Role

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SUMMARY

The hyperglycemic and hyperglucagonemic effects of systemically administered neurotensin in rats were investigated to explore the possibility that they are mediated by histamine and to determine whether neurotensin might have a role in the mediation of the responses to central nervous system glucopenia. The hyperglycemic response to neurotensin was partially blocked by the histamine H-1 receptor blockers, diphenhydramine and promethazine, and by the H-2 receptor blocker, cimetidine. The hyperglucagonemic response was completely blocked by diphenhydramine and promethazine and only partially blocked by cimetidine. The effects of histamine on glucose, glucagon, and insulin secretion were similar to those of neurotensin, and the inhibitory effects of both H-1 and H-2 blockers were comparable. The stimulatory effect of histamine on insulin secretion observed after adrenal autotransplantation was also similar to that previously reported for neurotensin. Neither antineurotensin serum nor diphenhydramine, however, was effective in blocking the hyperglycemic and hyperglucagonemic responses to the central administration of 2-deoxyglucose. The results are consistent with a histamine mediation of the effects of exogenously administered neurotensin but do not support a proposed role for neurotensin or histamine in the mediation of the hyperglycemic and hyperglucagonemic responses to central glucopenia. DIABETES *27*:577-82, May, 1978.

We have previously reported that neurotensin, a hypotensive tridecapeptide isolated from bovine hypothalamus,[1] elicits a hyperglycemic response associated with hyperglucagonemia following systemic injection.[2] The hyperglycemic response was shown to be due to catecholamine- as well as glucagon-mediated effects. The absence of an increase in insulin secretion in the presence of hyperglycemia was attributed to an adrenal-medulla-mediated inhibitory effect, since hyperinsulinemia was observed in response to neurotensin after adrenal autotransplantation (functional demedullation).

It has recently been reported that the glucagon-releasing effects of substance P, a sialagogic undecapeptide,[3] and of neurotensin could be blocked by diphenhydramine,[4] raising the possibility that their effects were mediated by histamine. The present studies were therefore performed to investigate this possibility by comparing the effects of neurotensin with those of histamine and by observing the effects of histamine receptor antagonists. In addition, evidence was sought for a possible physiologic role of neurotensin in mediating the hyperglycemic response to central glucopenia.

METHODS

Animals and Experimental Procedures

Male Holtzman rats weighing 250 to 350 gm. were used for all experiments except for those on adrenal autotransplantation, where animals weighed 450 to 550 gm. Animals were maintained in a temperature-controlled (23° C.), 14-hour-light–10-hour-dark–cycled room and given tap water and food (Wayne Lab-Blox) ad libitum. Food was removed two hours before the start of each experiment.

A PE-50 catheter was inserted into the carotid artery under pentobarbital (35 mg./kg., intraperitoneally) anesthesia for injection and sampling. After a 20-minute stabilization period, a 0.7-ml. blood sample (at 0 minute) was withdrawn and immediately chilled in a tube containing heparin and Trasylol (500 U./ml.). Neurotensin (2.5 μg./kg.), histamine (4

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mg./kg.), or saline was then injected in a volume of 1 ml. per kilogram through the catheter, and additional blood samples were collected at 15 minutes and, in some experiments, at 30 minutes after the injection. Diphenhydramine hydrochloride (4 mg./kg.), promethazine hydrochloride (2 mg./kg.), cimetidine (4 mg./kg.), or saline was injected intraperitoneally 15 minutes before the injection of neurotensin or histamine.

Adrenal autotransplantation was performed by excising both adrenals and suturing them to the adjacent muscle four months before the experiment. Following this operation, the adrenal medulla degenerates while the cortex revascularizes and regains glucocorticoid-secretory activity within two weeks.

In the experiments employing central 2-deoxyglucose administration, a PE-10 catheter was implanted into the lateral cerebral ventricle and an indwelling catheter was implanted into the external jugular vein at least three days before the experiment by previously described techniques.[5,6] No anesthesia was used in these experiments.

Neurotensin Antiserum

Antiserum to synthetic neurotensin was prepared in rabbits by repeated injections of a neurotensin-diisothiocyanate-bovine serum albumin complex, the details of which will be described in a separate communication. Serum obtained seven months after immunization was used for the passive immunization experiments. Antiserum or normal serum (1 ml.) was injected intravenously two minutes before the injection of neurotensin or of 2-deoxyglucose.

Glucose and Hormone Measurements

Plasma glucose was measured by the ferricyanide method[7] on a Technicon AutoAnalyzer. Plasma insulin was measured by a double-antibody radioimmunoassay[8] using a porcine insulin standard. Plasma glucagon was measured by a double-antibody radioimmunoassay using 30 K antiglucagon serum and a bovine-porcine standard, as previously described.[2]

Reagents

Diphenhydramine hydrochloride (Benadryl, Parke Davis), promethazine hydrochloride (Phenergan, Wyeth Laboratories), and histamine (Sigma Chemical Company) were each purchased. Synthetic neurotensin was generously provided by Dr. Susan Leeman and by Dr. Roger Guillemin. Cimetidine was generously supplied by John G. Paul, of Smith Kline and French Laboratories.

Statistical Analyses

Differences between groups were determined by the Mann-Whitney U test.[9] Values of $p < 0.05$ were considered significant.

RESULTS

Effect of Histamine Receptor Antagonists on Neurotensin Hyperglycemia

The effect of diphenhydramine (4 mg./kg., intraperitoneally), a histamine H-1 receptor antagonist, on the hyperglycemic effects of neurotensin (2.5 μg./kg., intra-arterially) is shown in figure 1. Neurotensin, administered alone, elicited a hyperglycemic ($p < 0.01$) and a hyperglucagonemic ($p < 0.025$) response at 15 and 30 minutes without a concomitant rise in plasma insulin, as previously reported.[2] Diphenhydramine pretreatment completely inhibited the hyperglucagonemic response at 15 minutes ($p < 0.025$) and partially blocked the hyperglycemic response at 15 and 30 minutes ($p < 0.025$). Plasma insulin levels remained unaltered despite the moderate hyperglycemic response in diphenhydramine-pretreated animals. Initial values for plasma glucose, insulin, and glucagon, indicated in the legend to figure 1, were similar in all experiments, with the exception of those in adrenal-autotransplanted animals.

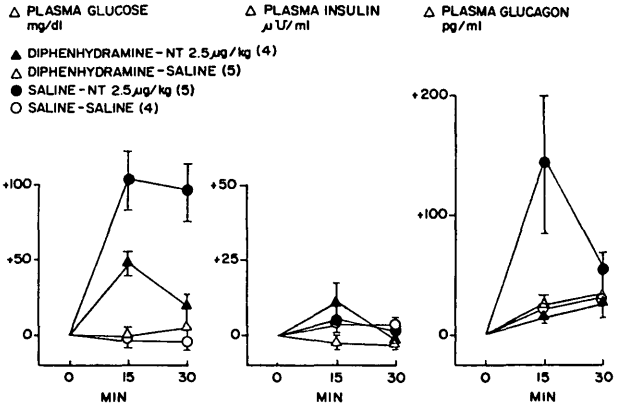

FIG. 1. Effect of diphenhydramine (4 mg./kg.) on the plasma glucose, insulin, and glucagon responses to the intra-arterial injection of neurotensin (2.5 μg./kg.). Shown are the means ± S.E.M. The numbers of animals are shown in parentheses. Preinjection values in saline-saline, neurotensin-saline, saline-diphenhydramine, and neurotensin-diphenhydramine groups were glucose—121 ± 6, 119 ± 5, 116 ± 5, and 123 ± 2 mg./dl.; insulin—14 ± 4, 20 ± 6, 19 ± 1, and 15 ± 2 μU./ml.; glucagon—73 ± 23, 85 ± 22, 63 ± 15, and 45 ± 8 pg./ml.

The effect of promethazine (2 mg./kg., intraperitoneally), another histamine H-1 receptor antagonist structurally unrelated to diphenhydramine, on neurotensin hyperglycemia is shown in table 1. As

with diphenhydramine, promethazine completely blocked the hyperglucagonemic response and partially inhibited the hyperglycemia. The slight rise in plasma insulin after neurotensin alone was unaltered by promethazine pretreatment.

TABLE 1

Effect of promethazine on plasma glucose, insulin, and glucagon responses to neurotensin

Group	Treatment	N	Δ Glucose (mg./dl.)	Δ Insulin (μU./ml.)	Δ Glucagon (pg./ml.)
I	Saline-saline	6	−3 ± 7	−3 ± 4	29 ± 13
II	Saline-NT	5	109 ± 8*	12 ± 7	155 ± 68†
III	Promethazine-saline	5	−5 ± 5	−1 ± 4	30 ± 17
IV	Promethazine-NT	8	25 ± 6	14 ± 4	23 ± 6

Promethazine (2 mg./kg.) or saline was administered intraperitoneally 15 minutes before the intra-arterial injection of neurotensin (NT, 2.5 μg./kg.) or saline. Shown are the means ± S.E.M. of the differences between glucose and hormone levels immediately before and 15 minutes after NT injection.

*$P < 0.01$ vs. group I and group IV.

†$P < 0.025$ vs. group I; $p < 0.01$ vs. group IV.

The effect of cimetidine (4 mg./kg., intraperitoneally), a histamine H-2 receptor blocker, on the effects of neurotensin is shown in table 2. Cimetidine only partially blocked the hyperglucagonemic and hyperglycemic responses to neurotensin. The addition of diphenhydramine to cimetidine resulted in a complete inhibition of the glucagon response to neurotensin, but there was no additional inhibition of the hyperglycemic response. There were no significant changes in plasma insulin in any of the treatment groups.

TABLE 2

Effect of cimetidine alone and together with diphenhydramine on plasma glucose, insulin, and glucagon responses to neurotensin

Group	Treatment	N	Δ Glucose (mg./dl.)	Δ Insulin (μU./ml.)	Δ Glucagon (pg./ml.)
I	Saline-saline	4	2 ± 5	0 ± 11	31 ± 6
II	Saline-NT	5	106 ± 13*	6 ± 10	96 ± 30†
III	Cimetidine-saline	6	−11 ± 3	−7 ± 3	18 ± 19
IV	Cimetidine-NT	5	57 ± 18	10 ± 7	49 ± 17
V	Cimetidine + diphenhydramine-NT	6	56 ± 12	−1 ± 3	17 ± 8

Cimetidine (4 mg./kg.) ± diphenhydramine (4 mg./kg.) or saline was administered intraperitoneally 15 minutes before the intra-arterial injection of neurotensin (NT, 2.5 μg./kg.) or saline. Shown are the means ± S.E.M. of the differences between glucose and hormone concentrations immediately before and 15 minutes after NT injection.

*$P < 0.025$ vs. groups I and V; $p < 0.1$ vs. group IV.

†$P < 0.025$ vs. group I; $p < 0.01$ vs. group V.

Effect of Histamine on Plasma Glucose, Insulin, and Glucagon Concentrations

In order to determine the possible mediation of histamine in the neurotensin responses, the effects of histamine on plasma glucose, insulin, and glucagon were studied. As shown in table 3, the intra-arterial injection of histamine (4 mg./kg.) elicited changes in plasma glucose, insulin, and glucagon similar to those seen after neurotensin, consisting of a hyperglycemic ($p < 0.01$) and hyperglucagonemic ($p < 0.01$) response with no change in plasma insulin. Pretreatment with diphenhydramine (4 mg./kg.) completely blocked the glucagon response but only partially inhibited the hyperglycemia. Pretreatment with cimetidine, 4 mg./kg. (table 4), partially inhibited both the hyperglycemic ($p < 0.025$) and hyperglucagonemic ($p < 0.05$) responses to histamine, whereas the absence of an insulin response to the hyperglycemia was unaltered.

TABLE 3

Effect of histamine and diphenhydramine on plasma glucose, insulin, and glucagon concentrations

Group	Treatment	N	Δ Glucose (mg./dl.)	Δ Insulin (μU./ml.)	Δ Glucagon (pg./ml.)
I	Saline-saline	6	−5 ± 5	5 ± 4	46 ± 11
II	Saline-histamine	6	122 ± 14*	4 ± 5	145 ± 25*
III	Diphenhydramine-saline	6	−9 ± 5	−5 ± 5	25 ± 11
IV	Diphenhydramine-histamine	7	38 ± 10†	2 ± 3	31 ± 6

Diphenhydramine (4 mg./kg.) or saline was injected intraperitoneally 15 minutes before the intra-arterial injection of histamine (4 mg./kg.) or saline. Shown are the means ± S.E.M. of the differences between glucose and hormone concentrations immediately before and 15 minutes after histamine injection.

*$P < 0.01$ vs. group I and group IV.

†$P < 0.01$ vs. group III.

TABLE 4

Effect of histamine and cimetidine on plasma glucose, insulin, and glucagon concentrations

Group	Treatment	N	Δ Glucose (mg./dl.)	Δ Insulin (μU./ml.)	Δ Glucagon (pg./ml.)
I	Saline-saline	5	−7 ± 4	−14 ± 14	25 ± 9
II	Saline-histamine	7	162 ± 12*	1 ± 13	169 ± 42*
III	Cimetidine-saline	5	−13 ± 1	15 ± 10	12 ± 7
IV	Cimetidine-histamine	5	117 ± 13†‡	−3 ± 12	89 ± 22†§

Cimetidine (4 mg./kg.) or saline was injected intraperitoneally 15 minutes before the intra-arterial injection of histamine (4 mg./kg.) or saline. Shown are the means ± S.E.M. of the differences between glucose and hormone concentrations immediately before and 15 minutes after histamine injection.

*$P < 0.01$ vs. group I.

†$P < 0.01$ vs. group III.

‡$P < 0.025$ vs. group II.

§$P < 0.05$ vs. group II.

The possible mediation of the adrenal medulla in the response to histamine was studied by determining the effects of histamine after adrenal demedullation (achieved by adrenal autotransplantation). Hyperglycemic and hyperglucagonemic responses to histamine were maintained in transplanted animals (table 5), and, in addition, a pronounced insulin response was also noted.

TABLE 5

Effect of histamine on plasma glucose, insulin, and glucagon concentrations in adrenal-autotransplanted rats

Group	Treatment	N	Δ Glucose (mg./dl.)	Δ Insulin (μU./ml.)	Δ Glucagon (pg./ml.)
I	Saline	5	−3 ± 9	−1 ± 4	53 ± 18
II	Histamine (4 mg./kg.)	5	136 ± 16*	111 ± 34	374 ± 162*

Shown are the means ± S.E.M. of the differences between glucose and hormone concentrations immediately before and 15 minutes after the intra-arterial injection of histamine. Preinjection values in groups I and II were: glucose—132 ± 10 and 132 ± 2 mg./dl.; insulin—20 ± 6 and 17 ± 5 μU./ml.; glucagon—124 ± 29 and 124 ± 29 pg./ml., respectively.

*$P < 0.01$ vs. group I.

Effect of Antineurotensin Serum on Neurotensin and 2-Deoxyglucose Hyperglycemia

The effect of antineurotensin serum on the hyperglycemic response to neurotensin was examined by injecting the animals with 1 ml. of antiserum or normal serum two minutes before the injection of neurotensin (2.5 μg./kg.). The binding capacity of the antiserum was 1.2 μg./ml., as determined by Scatchard analysis with ^{125}I-neurotensin (to be published). Partial suppression of the hyperglycemic response to neurotensin was observed in the antiserum-treated animals at 15 minutes (Δ plasma glucose: 100 ± 8 mg./dl. in antiserum-treated vs. 63 ± 2 mg./dl. in normal-serum-treated, $p < 0.01$). The effects of the antiserum on the hyperglucagonemic response could not be measured because the injection of rabbit antineurotensin serum resulted in plasma levels of rabbit IgG sufficient to interfere with the glucagon radioimmunoassay, which employed a rabbit anti-glucagon serum.

The effect of antineurotensin serum on 2-deoxyglucose hyperglycemia was next determined by injecting antineurotensin serum or normal serum (1 ml.) intravenously two minutes before the central injection of 2-deoxyglucose (8 mg./20 μl.) through a previously implanted lateral cerebroventricular catheter in unanesthetized animals. As shown in table 6, 2-deoxyglucose hyperglycemia was not suppressed by antineurotensin serum. Plasma glucagon responses could not be measured in this experiment for similar reasons.

TABLE 6

Effect of antineurotensin serum on the hyperglycemic response to the central administration of 2-deoxyglucose

Group	Treatment	N	Δ Plasma glucose, mg./dl. +5 min.	+15 min.	+30 min.
I	Normal serum, 2-DG	5	25 ± 3	41 ± 4	109 ± 6
II	Antineurotensin serum, 2-DG	4	18 ± 5	44 ± 9	88 ± 16

Antineurotensin or normal serum (1 ml.) was injected intra-arterially two minutes before the injection of 2-deoxyglucose (2-DG, 8 mg./20 μl.) through a previously implanted catheter in the lateral cerebral ventricle. Shown are the means ± S.E.M.

Effect of Diphenhydramine on the Glucose, Insulin, and Glucagon Responses to Central 2-Deoxyglucose

Since diphenhydramine was capable of inhibiting the hyperglycemic and hyperglucagonemic responses to neurotensin, its effect on the response to central 2-deoxyglucose was studied. Intraperitoneal administration of diphenhydramine (4 mg./kg.) 15 minutes before the cerebroventricular injection of 2-deoxyglucose (8 mg./20 μl.) did not inhibit the hyperglycemic or hyperglucagonemic responses to 2-deoxyglucose (table 7). Diphenhydramine was also without effect on the inhibitory action of 2-deoxyglucose on insulin secretion.

DISCUSSION

In the short period since the isolation and charac-

TABLE 7

Effect of diphenhydramine on the plasma glucose, insulin, and glucagon responses to central 2-deoxyglucose administration

Group	Treatment	N	Δ Glucose, mg./dl. 15 min.	30 min.	Δ Insulin, μU./ml. 15 min.	30 min.	Δ Glucagon, pg./ml. 15 min.	30 min.
I	Saline, 2-DG	4	69 ± 23	94 ± 7	−4 ± 6	−7 ± 7	140 ± 31	172 ± 31
II	Diphenhydramine, 2-DG	5	66 ± 16	132 ± 18	−4 ± 2	4 ± 3	196 ± 36	241 ± 86

Diphenhydramine (4 mg./kg.) or saline was injected intraperitoneally 15 minutes before the central administration of 2-deoxyglucose (2-DG, 8 mg./20 μl.) through a previously implanted catheter in the lateral cerebral ventricle. Shown are the means ± S.E.M.

terization of neurotensin, numerous reports describing its effects on carbohydrate metabolism have appeared. Carraway and Leeman first reported the hyperglycemic effects, which were accompanied by an increase in glycogen phosphorylase, a reduction in hepatic glycogen content and unaltered disappearance of ^{14}C-glucose from plasma.[10,11] We[2] and Brown and Vale[3] subsequently reported that neurotensin stimulates glucagon secretion by a mechanism that appeared to be independent of the adrenal. A relative inhibition of insulin secretion following neurotensin was shown to be adrenal-medulla-mediated in that it could not be demonstrated following adrenal autotransplantation. These findings are similar to those observed in response to electric stimulation of the ventromedial hypothalamus[12] and to the central administration of 2-deoxyglucose[13] and suggested the possibility that neurotensin might be a factor in the mediation of the response to central glucopenia. The role of neurotensin as a central mediator appeared unlikely because of the ineffectiveness of this peptide when injected into the lateral cerebral ventricle.[2] Thus, attention was focused on a peripheral site(s) of action for neurotensin, a possibility that became more attractive when the presence of neurotensin was reported outside of the central nervous system.[14] The observation that the glucagon-releasing effect of neurotensin was blocked by diphenhydramine[4] also raised the possibility of histamine participation in the neural regulation of carbohydrate metabolism.

The present results have indicated many similarities between the responses to neurotensin and to histamine. Both evoke a hyperglycemic response, stimulate glucagon release, and impair the insulin response to hyperglycemia. The glucagon-releasing effects of both are independent of the adrenal medulla, and the inhibition of insulin secretion due to histamine as well as to neurotensin is eliminated by adrenal autotransplantation. The inhibition of the glucagon-releasing effects of both compounds by the H-1 blocker, diphenhydramine, was consistent with a histamine mediation of the neurotensin effects but could also be explained by an effect of diphenhydramine on the neurotensin receptor. The similarity of the inhibitory effects of a second H-1 receptor antagonist, promethazine, which is chemically distinct from diphenhydramine, and of cimetidine, an H-2 receptor antagonist, however, is evidence for the mediation of neurotensin effects by histamine. The results of the histamine-blocker experiments suggest that the receptor responsible for the stimulation of glucagon secretion is completely blocked by H-1 antagonists but only partially by H-2 antagonists.

There is also evidence from other studies to link the actions of neurotensin and histamine. Both cause hypothermia after central administration,[15,16] both are present in high concentrations in the hypothalamus, the gastrointestinal tract, and postganglionic sympathetic fibers,[17,18] and both have hypotensive effects and increase capillary permeability.

The possible role of endogenous neurotensin in mediation of the response to central glucopenia was examined with both a specific antineurotensin serum and diphenhydramine. The antineurotensin serum used was of sufficient potency to inhibit partially the injection of a dose of neurotensin calculated to produce a plasma neurotensin level of 80 ng./ml. immediately after injection (based on a plasma volume equal to 3 per cent of body weight). The same dose of antiserum was, however, without effect on the hyperglycemic response to 2-deoxyglucose. Since plasma levels of neurotensin have been reported to be nearly 10^3 times as low,[14] the results raise doubts as to the possibility that circulating neurotensin is operative in the response to 2-deoxyglucose.

Since neurotensin mediation might not require the presence of the peptide in circulating plasma but could occur on the basis of cell-to-cell communication, such as has been suggested for somatostatin, we attempted to inhibit the response to 2-deoxyglucose with diphenhydramine, using a dose that was shown capable of inhibiting the response to exogenous neurotensin. The response to 2-deoxyglucose included an increase in plasma glucagon levels, as we have also shown to occur in the dog,[19] as well as a rise in plasma glucose. The ineffectiveness of diphenhydramine in suppressing the glucose or glucagon responses to 2-deoxyglucose provides further evidence that neurotensin, and also histamine, are not factors in the mediation of the response to central glucopenia.

In summary, the results indicate many similarities between the effects of exogenously administered neurotensin and those of histamine and suggest that some, though not all, of the effects of neurotensin are mediated by histamine through a receptor exhibiting both H-1 and H-2 properties. The results, however, do not support a proposed role for endogenous neurotensin in mediating the response to central glucopenia. Moreover, they indicate the need for caution in interpolating the results of experiments using pharmacologic quantities of endogenously occurring substances to propose a role for these compounds

under physiologic conditions.

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