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Blood Glucose Is Correlated with Cerebrospinal Fluid Neurotransmitter Metabolites

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Abstract
Medications which influence monoaminergic neurotransmission can also have an effect on glucose regulation. In order to better understand the role of central monoaminergic neurotransmission in blood glucose homeostasis, we explored the relation between blood glucose and cerebrospinal fluid metabolite concentrations of monoaminergic neurotransmitters. Under stringently controlled resting conditions, we measured fasting blood glucose and performed lumbar punctures on 41 healthy participants. Peripheral blood glucose concentrations were significantly correlated with the cerebrospinal fluid concentrations of the dopamine metabolite, homovanillic acid and the noradrenaline metabolite, 3-methoxy-4-hydroxyphenylglycol. These correlations may represent a homeostatic relation between brain neurotransmitter activity and blood glucose.

Introduction

There is a growing awareness that medications affecting monoaminergic neurotransmission can have significant effects on glucose regulation. Antipsychotics are increasingly associated with iatrogenic diabetes [1], while hypoglycemia has been associated with other drugs, such as anti-parkinsonian agents [2] and serotonergic antidepressants [3]. It is possible that these medications are altering glucose homeostasis through their effect on the brain. The brain can directly regulate the concentration of peripheral blood glucose via innervation of the liver as well as via hormonal intermediaries [4]. An important component of this regulation is the ventral medial hypothalamus, which functions as a central glucose sensor, and can increase hepatic glucose production by stimulating both the autonomic nervous system and the endocrine system [5, 6]. This hypothalamic control of blood glucose is influenced by noradrenergic, serotonergic, and dopaminergic neurotransmitter systems [4].

Noradrenergic activity in the hypothalamus exerts a prominent influence on glucose regulation. Activation of the noradrenergic system is linearly related to the concentration of glucose in the blood. Hypothalamic noradrenergic activity is stimulated by neuroglycopenia but suppressed by excess glucose, suggesting that glucose or a glucose metabolite provides a negative feedback signal to the hypothalamus [7]. Because other sites of noradrenergic activity, such as the locus coeruleus, are stimulated by

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hypoglycemia [8], it is possible that a more generalized central mechanism could also increase circulating glucose [9].

In addition to hypothalamic serotonergic activity [4, 5, 10], serotonergic activity originating in the raphe nucleus also regulates glucose homeostasis. This central area of serotonergic activity is associated with activation of the sympathoadrenomedullary system [5] which can affect peripheral glucose mobilization. Serotonergic involvement in blood glucose regulation is also suggested by the positive effect of some serotonin reuptake inhibitors on glucose regulation in diabetics [11, 12], a potentially important feature considering the frequent association of depression with diabetes [13].

The basis for dopaminergic involvement in glucoregulation is illustrated by the increase in peripheral glucose produced by central dopamine receptor stimulation [14], and the suppressive effect of hypoglycemia on firing of dopamine containing neurons [15]. Brain disorders associated with pathological alterations in dopaminergic function such as Parkinson's disease [16], tardive dyskinesia [17, 18], and schizophrenia [19] are associated with impaired peripheral glucose metabolism. Some antipsychotic medications can cause hyperglycemia and diabetes [1, 20, 21]. Although the mechanism for this is unknown, antipsychotics act prominently as dopamine receptor antagonists, with variable actions on other neurotransmitter systems [22]. Preliminary evidence indicates that bromocriptine (a dopamine agonist) can significantly improve glucose regulation in diabetics [2, 23].

Considering the above evidence for monoaminergic involvement in blood glucose regulation, as well as the importance of blood glucose in supplying brain metabolic needs, we postulated that measures of brain activity (i.e., measures of neurometabolite activity) might be directly related to the level of blood glucose. Such a relation is suggested by the relation between glucose and neurotransmitter activity in discrete areas of the hypothalamus [7], and the generalized correlation of activity of norepinephrine, serotonin and dopamine in the central nervous system (CNS) [24]. The interaction of the activity of these neurotransmitters in relation to peripheral blood glucose regulation has never been evaluated in humans. When studying monoaminergic neurotransmitter systems in humans, metabolite concentrations in cerebrospinal fluid (CSF) can provide an index of neurotransmitter activity in the brain [25]. There is a time lag for neurotransmitter metabolic products originating in the brain to appear in the lumbar CSF, which makes this sampling site appropriate for studying CNS neurotransmitter activity under steady-state conditions [26–28]. In a cross-sectional observational study of healthy participants, we compared fasting blood glucose concentrations with the concentrations of the CSF metabolites of noradrenaline, 3-methoxy-4-hydroxyphenylglycol (MHPG), of dopamine, homovanillic acid (HVA), and of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). The aim of this study was to explore the collective activity of these neurotransmitter systems in relation to blood glucose homeostasis.

Methods

The study sample consisted of 33 male and 8 female healthy volunteers. All participants were in excellent physical and mental health, had no history of alcohol or drug abuse, and had normal fasting blood glucose. Each participant gave written informed consent as approved by the National Institute on Alcoholism and Alcohol Abuse Institutional Review Board and was paid for his participation. In order to minimize the potential confounding affects that certain foods can have on neurometabolite analysis, all participants were on a low-monoamine diet [29] for 3 days prior to the lumbar puncture. All participants were studied as inpatients on the National Institute on Alcoholism and Alcohol Abuse ward at the National Institutes of Health Clinical Center, where they fasted overnight prior to study. On the morning of the study, they remained in bed except for a brief use of the rest room at approximately 07:00 h. At approximately 09:30 h, blood for glucose was collected by venipuncture immediately before the lumbar puncture. The lumbar puncture was performed in the left lateral decubitus position, and the first 12 ml of CSF were collected in a single aliquot, thoroughly mixed, and immediately placed on wet ice and quickly stored at –70 °C. Analysis of CSF neurometabolites was accomplished using high-pressure liquid chromatography following standardized procedures [30]. Within and between run coefficients of variance of the assay values were <10%. The Statistica (Statsoft, Tulsa, Okla., USA) software for personal computer was used for data analysis. A p value ≤ 0.05 was considered statistically significant.

Results

The average age of the subjects was 37.1 ± 13.6 (range 20–75), the average height was 174 ± 9.3 cm (range 152–200) and the average weight was 76.2 ± 10.0 kg (range 53–96). The concentrations (mean ± SD) of the CSF neurotransmitters and blood glucose were as follows: HVA 192 ± 74 pmol/ml, MHPG 40 ± 12 pmol/ml, 5-HIAA 96 ± 35 pmol/ml, and peripheral glucose 92 ± 7 mg/dl. Correlations were performed to examine the relations among the neurotransmitters and age, height, weight, and blood glucose. The only variables significantly correlated with blood glucose were HVA: $r = 0.37$, $p = 0.017$, $n = 41$ (fig. 1) and MHPG: $r = 0.52$, $p = 0.001$, $n = 41$ (fig. 2). The correlation of glucose with 5-HIAA was $r = 0.19$, $p =$

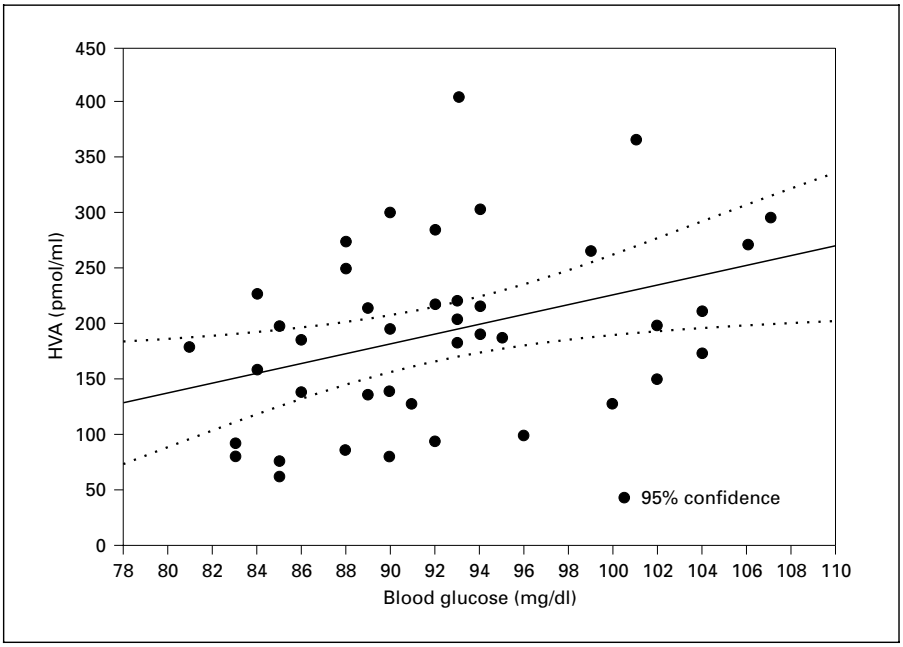

Fig. 1. Cerebrospinal fluid homovanillic acid (HVA) and fasting blood glucose concentration, r = 0.37, p = 0.017, n = 41.

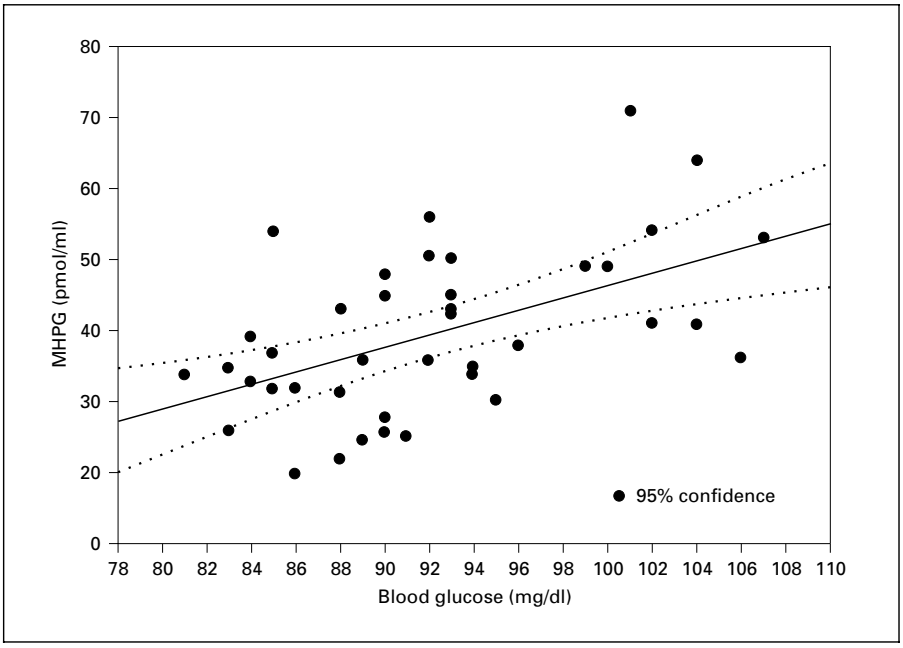

Fig. 2. Cerebrospinal fluid 3-methoxy-4-hydroxyphenylglycol (MHPG) and fasting blood glucose concentration, r = 0.52, p = 0.001, n = 41.

0.212, n = 41. Neurotransmitters were significantly correlated with each other: 5-HIAA vs. HVA, r = 0.69, p < 0.001, n = 41; 5-HIAA vs. MHPG, r = 0.31, p = 0.048, n = 41, and HVA vs. MHPG, r = 0.31, p = 0.042, n = 41. Regression analysis with blood glucose as the dependent variable and CSF concentrations of HVA and MHPG as independent variables resulted in an $R^2 = 0.31$ and a significant F(2,38) = 8.7, p = 0.001.

Discussion

In this study, we found a statistically significant correlation between blood glucose and CSF concentrations of both HVA and MHPG. The correlation of glucose with 5-HIAA was not statistically significant. Our findings support the postulate that an association exists between brain monoaminergic neurotransmitter activity and blood glu-

cose in humans. The high correlation noted between glucose and MHPG is consistent with prior studies [27, 31] and may be due to the fact that central noradrenergic neural pathways are directly involved in the regulation of glucose release by the liver and can indirectly inhibit pancreatic insulin release through activation of adrenal medullary catecholamines. Unlike 5-HIAA and HVA, a substantial proportion of MHPG in CSF may be derived from blood and peripheral sympathetic activity [32]. Since peripheral sympathetic activity can affect blood glucose levels, this factor could possibly explain the strong association of MHPG with blood glucose relative to the other neurotransmitters. Peripheral sympathetic activity cannot account for all of our findings, however, as the dopamine metabolite HVA was also correlated with blood glucose.

Because the samples were obtained in the fasting state, and after an overnight bedrest, these results reflect a homeostatic association rather than imply causation. Specifically, these results do not indicate that neurotransmitter levels are regulating peripheral glucose level any more than they indicate that peripheral glucose is driving brain metabolic activity. However, our data are consistent with either possibility. If they reflect blood glucose modulation of brain metabolic activity, our findings would be consistent with the evidence that glucose is an activator of brain function, as illustrated by the reported ability of increased blood glucose to improve memory, attention, psychological functioning, and reaction to frustration [33–35]. Also, our findings would be consistent with the alterations in brain monoamine metabolism found in rats rendered diabetic by streptozotocin [36]. If, on the other hand, our results reflect neurotransmitter regulation of blood glucose, our findings illustrate the potential for monoaminergic drugs to modulate blood glucose. One model for neurotransmitter control of blood glucose consistent with our findings is that promoted by Agnati et al. [37]. In that model, brain signaling can occur by relatively slow nonsynaptic transmission in a three-dimensional mode within the extracellular fluid. This is a global regulation of entire neural networks that can involve monoaminergic neurotransmitters. Agnati et al. contrast this with neurotransmission that occurs via fast direct synaptic transmission involving presynaptic knob/synaptic cleft/postsynaptic membrane, a more precise mechanism of signal transduction perhaps less likely to produce detectable levels of neurometabolites in the CSF. It is likely, however, that both mechanisms are operative in the regulation of blood glucose, considering the evidence that hypothalamic glucose sensors are important in blood glucose regulation [5, 38, 39]. For example, serotonin can act in the hypothalamus to potentiate noradrenergic activity and interacts to produce hyperinsulinemia, insulin resistance and glucose intolerance [40]. Such serotoninergic activity, acting via fast direct synaptic transmission, is unlikely to be detected in the CSF.

Additional studies are needed to fully understand the significance of the relation between blood glucose and neurotransmitter metabolites. One possibility is that it is driven by substances related to glucose such as insulin [41, 42]. Peripheral insulin can affect neurotransmitter metabolism by influencing the brain uptake of amino-acid precursors [43], and intracerebroventricularly administered insulin can decrease rat brain dopamine and noradrenaline levels [44]. Noradrenergic metabolism in the rat brain, as indicated by MHPG, can be increased by hyperinsulinemic, euglycemic clamp [45]. Changes in monoaminergic neurotransmitters in the hypothalamus can also induce dysregulation of pancreatic islet cell insulin release in response to glucose [46]. Examining changes in CSF neurometabolites while manipulating glucose, insulin and triglyceride levels might elucidate the basis of the relations that we observed. It should be noted that given the methodology employed in the present study, it was not possible to ascertain to what degree the relationship between glucose and HVA arises from dopaminergic neurons or from dopamine co-release from noradrenergic neurons, a phenomenon that can occur in noradrenergic neurons [47]. If peripheral blood glucose is exerting an influence on neurotransmitter activity, it might be an important confounding factor when studying CSF monoamine neurotransmitter metabolites. Improved understanding of the relationship between peripheral glucose and neurotransmitter activity may uncover unknown factors important in the regulation of blood glucose, appetite and brain function, and allow for the design of improved pharmacotherapies with less potential for adverse effects on glucose homeostasis [11].

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