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ORIGINAL INVESTIGATION

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Effects of pharmacological doses of 2-deoxyglucose on plasma catecholamines and glucose levels in patients with schizophrenia

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Abstract *Rationale:* Several lines of evidence suggest that the pathophysiology of schizophrenia may be associated with altered noradrenergic and glucoregulatory function. *Objective:* The aim of this study was to investigate these alterations during a perturbed homeostatic state. *Methods:* Fifteen patients with schizophrenia and 13 healthy individuals were given a glucose deprivation challenge through administration of pharmacological doses of 2-deoxyglucose (2DG; 40 mg/kg), and their plasma was assayed over the next 60 min for concentrations of norepinephrine (NE), the intraneuronal NE metabolite dihydroxyphenylglycol (DHPG), epinephrine and glucose. *Results:* 2DG induced significant increases in plasma NE, epinephrine and glucose levels in both groups with significantly greater NE and glucose increments in patients than in controls. For DHPG, 2DG produced increases in patients and decreases in the control subjects. NE responses correlated positively and significantly with the DHPG and glucose responses in schizophrenics, but not in controls. *Conclusions:* These findings suggest that patients with schizophrenia have exaggerated NE and glucose responses to an acute metabolic perturbation.

Keywords Norepinephrine · Dihydroxyphenylglycol · Epinephrine · Glucose · 2-Deoxyglucose · Glucoprivation · Schizophrenia

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Introduction

Norepinephrine (NE) is the sympathetic neurotransmitter that plays a critical role in maintenance of homeostasis and rapid compensatory adjustments to physiological and psychological challenges. Numerous studies in both medicated (Naber et al. 1980; Sternberg et al. 1981; Gattaz et al. 1983; van Kammen et al. 1989, 1990; Thibaut et al. 1998; Farley et al. 1978; Crow et al. 1979) and unmedicated (Lake et al. 1980; Kemali et al. 1982; Sternberg et al. 1982; Glazer et al. 1987; van Kammen et al. 1989, 1990; Breier et al. 1990) patients with schizophrenia have noted elevated NE concentrations in samples obtained from plasma, cerebrospinal fluid (CSF; Lake et al. 1980; Naber et al. 1980; Sternberg et al. 1981; Kemali et al. 1982; Sternberg et al. 1982; Gattaz et al. 1983; Glazer et al. 1987; van Kammen et al. 1989, 1990; Breier et al. 1990; Thibaut et al. 1998) and postmortem brain (Farley et al. 1978; Crow et al. 1979; Bird et al. 1979a,b; Bridge et al. 1985; Powchik et al. 1998).

The pathophysiological significance of these findings remains unclear, in part because most studies of NE in schizophrenia have tended to be done during the resting or basal state. Given the regulatory function exerted by the sympathetic system on homeostasis, however, an experi-

mental paradigm examining noradrenergic activity during a perturbed homeostatic state may uncover a dysfunction that is unapparent during the resting condition.

One method to induce a metabolic perturbation (accompanied by a robust activation of the sympathoneural and related neuroendocrine/neurochemical systems) involves the use of glucose-depriving (glucoprivic) paradigms (Goldstein et al. 1992). These paradigms are especially relevant for schizophrenia because it was associated in prior studies with glucose metabolism irregularities, including impaired glucose tolerance (Finney 1989; Ryan et al. 2003), insulin resistance and a high prevalence of non-insulin-dependent diabetes mellitus (NIDDM; Mukherjee et al. 1996; Dixon et al. 2000; Ryan and Thakore 2002). While the basis of the glucoregulatory abnormalities in patients with schizophrenia is uncertain, they may relate to the patients' unhealthy life style (Kendler 1986), their poor fitness (Brown et al. 1999), their use of novel antipsychotic drugs (APDs; Kato and Goodnick 2001; Popkin and Colon 2001; Newcomer et al. 2002) and their increased adiposity (Ryan and Thakore 2002; Ryan et al. 2004; Banerji et al. 1997; Goodpaster et al. 1999).

Insulin is the primary glucoprivic agent, but its use may be confounded by only short-lived and rapidly counter-regulated (predominately by glucagon) hypoglycemia (Wyngaarden and Smith 1988). Additionally, insulin may hamper the distinction of primary homeostatic dysregulation from group differences in response to aversive physiological and psychological factors since it exaggerates sympathetic autonomic responses (Davis et al. 1993a,b) leading to marked anxiety and physical distress (Goldstein 1995).

Use of pharmacological doses of a non-metabolizable glucose analog, 2-deoxyglucose (2DG), can be an alternative technique to perturb the sympathoregulatory system. 2DG undergoes facilitated diffusion into cells via glucose transporters where it is phosphorylated by hexokinase to 2-deoxyglucose-6-phosphate (2DG-6-P) but is not metabolized further down the glycolytic pathway. When 2DG is given in pharmacological doses, the 2DG-6-P accumulates to levels that competitively inhibit glucose-6-phosphate dehydrogenase, resulting in transient disruption of glycolysis and interference with cellular utilization of glucose (Horton et al. 1973).

The central nervous system is especially sensitive to the effects glucoprivation due to its critical dependence on glucose for metabolic activity. For that reason, 2DG acts at the hypothalamus and other central sites to generate compensatory responses including sympathetic activation and hyperglycemia (Smythe et al. 1984; Storlien et al. 1985; Matsunaga et al. 1989; Smythe et al. 1989; Pascoe et al. 1989; Smythe and Edwards 1992; Gotoh et al. 2001; Niijima 1975; Gagner et al. 1985;Yoshimatsu et al. 1987; Takahashi et al. 1994, 1996). In addition, peripheral glucoreceptors in the portal vein (Hevener et al. 1997, 2000) may directly trigger NE release and produce a further rise in plasma glucose concentration by mobilizing liver glycogen stores (Brodows et al. 1975). Thus, 2DG results in a protracted (Niijima 1975; Gagner et al. 1985; Yoshimatsu et al. 1987; Gotoh et al. 2001; Takahashi et al. 1994, 1996) clinical state similar to hypoglycemia, even though it elevates plasma glucose levels (Breier 1989). Notwithstanding the above-mentioned neuroendocrine and metabolic effects, unlike insulin, 2DG evokes only mild subjective responses (i.e., hunger) and is well tolerated by patients with schizophrenia (Breier 1989)—a feature adding to more conclusive interpretation of findings.

In the present study, we compared the effects of 2DG administration on plasma levels of NE and glucose in patients with schizophrenia and healthy controls. To examine NE turnover in sympathetic nerves, we assayed the levels of the intraneuronal NE metabolite, dihydroxyphenylglycol (DHPG; Eisenhofer et al. 1992). In addition, epinephrine levels were measured to characterize the activity of the adrenomedullary system, a purported source of plasma NE during the 2DG-induced glucopenia in healthy subjects (Goldstein et al. 1992). Finally, given NE's potential role in glucoregulation (Skyler 2000), the relationship between plasma NE and glucose levels was also examined.

Methods

Subjects

Fifteen patients with schizophrenia and 13 healthy control subjects participated in this study after giving written informed consent to a National Institute of Health (NIH) Institutional Review Board-approved protocol. Diagnoses were determined by a diagnostic conference utilizing data from the Structured Clinical Interview for DSM-III-R (SCID), a clinical interview by a research psychiatrist, past psychiatric and medical records, and informants' interviews.

All patients were stable outpatients with a chronic course of illness [mean age at appearance of DSM-IV criterion A symptoms of schizophrenia±standard deviation (SD)=21.4±3.8 years; mean duration of the illness=15.3 ±9.0 years] and were tested during treatment with a stable dose of a typical APD for a minimum of 2 weeks (except one patient, who was treated for 8 days and two patients who entered the study APD free). NE and glucose data from the minimally treated and the drug-free subjects were within one SD from the rest of the schizophrenic participants. Drug and dose (chlorpromazine equivalent mean=748.5±501.3 mg/day, range 333–2000 mg/day) were varied to achieve a stable clinical condition. The baseline Brief Psychiatric Rating Scale (Overall and Gorham 1962) total symptom score (24-item scale; items rated 1–7) on the study day was 33±4.7, which is indicative of low to moderate symptom levels.

Healthy control subjects were recruited through the NIH normal volunteer program and had no psychiatric history as determined by SCID. All subjects had no history of illegal drugs/alcohol abuse or dependence, head trauma resulting in loss of consciousness or any major medical

illness or endocrinopathy. Their good physical health was ascertained by physical examination, electrocardiogram (EKG), screening blood work-up and urinalysis. There were no significant differences between schizophrenic and control subjects, respectively, for age (37.0±9.4 years versus 33.2±6.6 years; t=1.2; df=26; P=0.24), gender (male/female, 11/4 versus 11/2; χ^2=0.53; df=1; P=0.47) and body weight (79.0±14.3 kg versus 80±17.7 kg; t=0.15; df=26; P=0.88).

Clinical protocol

The study reported here was part of a protocol involving positron emission tomography (PET), and the neuroimaging results are reported elsewhere (Elman et al. 1999b). Although arterial blood sampling was primarily employed for quantification of the PET data, this sampling source, compared with venous blood, provides a better reflection of total body sympathetic nervous activity and glucose metabolism, since arm tissues may remove a substantial proportion of plasma NE and glucose (Folkow et al. 1983; Chang et al. 1986; Riggs et al. 1984).

On the morning of the procedure, the subjects were admitted to the 4E Unit of the Clinical Center, NIH, after having fasted and refrained from alcohol, tobacco, caffeine, or strenuous physical activity for at least 10 h. While in the supine position, an arterial catheter was inserted percutaneously after local anesthesia was given to the overlying skin. An intravenous catheter was placed into the antecubital fossa of the contralateral arm and was kept patent with a slow isotonic (0.9% w/v) saline drip. After a 90-min rest period, 2DG (40 mg/kg, maximal dose 4 g) in 50 ml isotonic saline solution was administered as an intravenous bolus. Continuous cardiac monitoring was performed throughout the course of the study. Self-ratings of sensation of hunger, thirst and distress were collected at baseline (before 2DG administration) and at the end of the study with a self-report visual analog rating scale, scored in millimeters (from the left side of a 100-mm line to a perpendicular mark made by the subjects at the point corresponding to their subjective impression). The scale items ranged from 0 mm (not at all) to 100 mm (extremely) with a "moderately" mark placed at 50 mm.

Biochemical variables

Arterial blood samples were collected in heparinized tubes at 30 min before (−30), immediately prior to bolus (0) and at +20, +40 and +60 min following the bolus and were placed on wet ice. After separation by refrigerated centrifugation at 4°C, the plasma was stored at −80°C. Plasma NE (the intraassay and interassay coefficients of variation were 6.5% and 1.9%, respectively), DHPG (the intraassay and interassay coefficients of variation were 8.4% and 3.7%, respectively) and epinephrine (the intraassay and interassay coefficients of variation were 3.0% and 11.4%, respectively) levels were assayed using liquid chromatography with electrochemical detection (Eisenhofer et al. 1986). Photometric assay with hexokinase (Tietz 1995) was used to measure plasma glucose (the intraassay and interassay coefficients of variation were 1.0% and 1.7%, respectively).

Statistical analyses

Data were analyzed using the statistical package Statistica (StatSoft, Inc., Tulsa, OK). NE, DHPG, epinephrine and glucose plasma concentrations at −30 min and 0 time points were averaged to constitute a single baseline value. To determine effects of glucoprivation on neurochemical, behavioral (self-ratings) and physiological (heart rate, blood pressure) variables, a one-way analysis of variance (ANOVA) with a repeated-measures design was conducted. Diagnosis (schizophrenia and healthy controls) was the grouping factor, and time (baseline, 20, 40 and 60 min) was the within-subjects factor. The non-parametric Spearman correlation coefficient was used for correlation analyses. Group data were summarized as mean ±SD. All analyses were two-tailed and a P value <0.05 defined statistical significance.

Results

There were no significant baseline differences between schizophrenic and control subjects in plasma NE (216.4 ±129.9 pg/ml versus 220.5±157.4 pg/ml; t=0.08; df=26; P=0.94) and glucose (98.5±11.2 mg/dl versus 95.4 ±9.1 mg/dl; t=0.8; df=26; P=0.43) levels. Throughout the 60 min following 2DG administration, both groups demonstrated robust increases (i.e., time effect) in plasma NE (F=20.97; df=3, 26; P<0.001) and glucose (F=68.5; df=3, 26; P<0.001) levels (Figs. 1, 2). Patients demonstrated significantly higher (group by time interaction) 2DG-induced NE (F=2.82; df=3, 26; P=0.04) and glucose (F=4.82; df=3, 26; P=0.004) levels, yielding mean change from the baseline of 309.6±257.1 pg/ml versus 124.2 ±223.7 pg/ml (t=2.0; df=26; P=0.05) for NE and 69.5 ±27.6 mg/dl versus 40.7±36.4 mg/dl (t=2.4; df=26; P=0.026) for glucose.

Table 1 displays the DHPG and epinephrine data. For DHPG, 2DG produced two different response profiles: increases in patients and decreases in the comparison subjects (respective mean change from the baseline: 107.8 ±257.1 pg/ml versus −89.3±223.7 pg/ml; t=2.24; df=26; P=0.03), resulting in a non-significant time effect (F=1.58; df=3, 26; P=0.20) and a significant group by time interaction (F=3.56; df=3, 26; P=0.018). Epinephrine data analyses revealed significant time effect (F=25.15; df=3, 26; P<0.001) and no group by time interaction (F=0.22; df=3, 26; P=0.88).

Patients, in comparison with controls, had significantly lower baseline hunger ratings (2.7±3.0 mm versus 5.1 ±2.1 mm; t=2.4; df=26; P=0.02), and other baseline data were not different between the groups. In all participants,

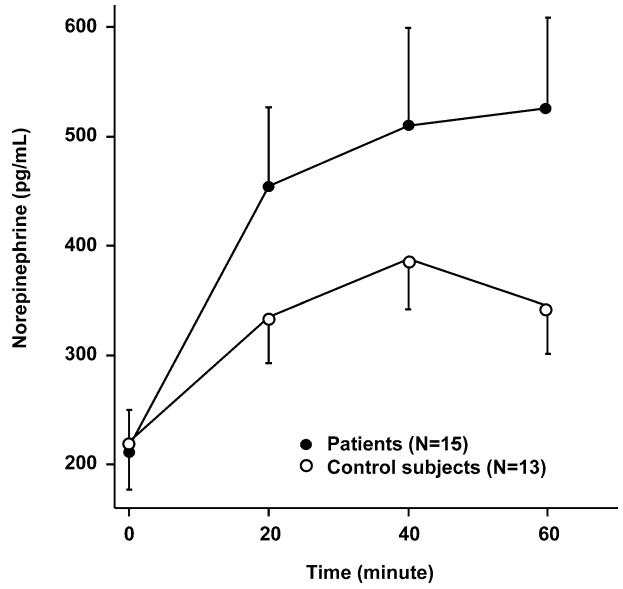

Fig. 1 The effects of pharmacological doses of 2-deoxyglucose on plasma norepinephrine levels in patients with schizophrenia and in healthy control subjects. Significant effect of time (F=20.97; df=3, 26; P<0.001) and group by time interaction (F=2.82; df=3, 26; P=0.04)

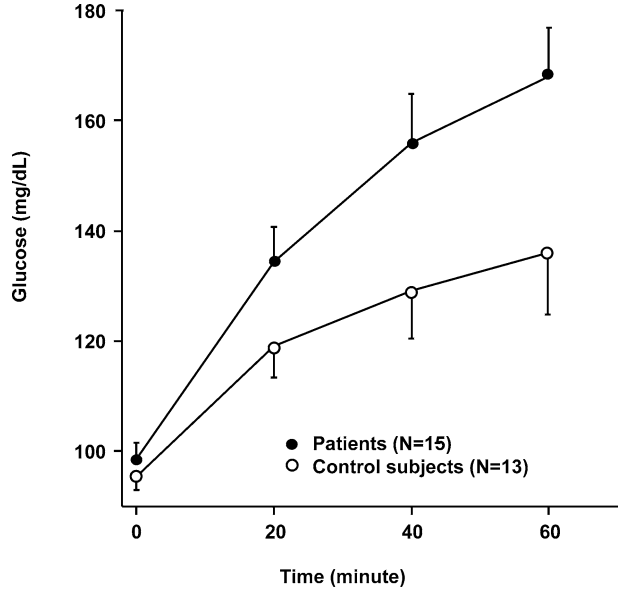

Fig. 2 The effects of pharmacological doses of 2-deoxyglucose on plasma glucose levels in patients with schizophrenia and in healthy control subjects. Significant effect of time (F=68.5; df=3, 26; P<0.001) and group by time interaction (F=4.82; df=3, 26; P=0.004)

2DG produced significant increases (time effect) in self-ratings of hunger (F=45.14; df=1,26; P<0.001), distress (F=7.59; df=1, 26; P=0.01) and thirst (F=23.53; df=1,26; P<0.001). The increases in the ratings for hunger (F=5.13; df=1, 26; P=0.03; mean change from the baseline: 5.7 ±3.0 mm versus 2.8±2.9 mm; t=2.6; df=26; P=0.016), but not thirst (F=0.0; df=1,26, 26; P=1.0) or distress (F=0.42; df=1,26, 26; P=0.52), were greater (group by time interaction) in the patient group.

Table 1 Effects of 2-deoxyglucose on plasma DHPG and epinephrine concentrations in patients with schizophrenia (N=15) and in healthy controls (N=13)

Time (min)	Catecholamine (pg/ml)	Patients	Controls
Baseline	DHPG	701.6 (46.3)	731.4 (119.4)
	Epinephrine	120.1 (47.3)	133.0 (53.9)
20	DHPG	744.6 (54.0)	731.7 (113.4)
	Epinephrine	1044.7 (161.7)	1225.4 (377.4)
40	DHPG	785.1 (61.5)	779.9 (118.6)
	Epinephrine	1153.2 (199.7)	1408.5 (449.7)
60	DHPG	809.4 (56.8)	642.1 (76.5)
	Epinephrine	1114.4 (157.4)	1259.8 (396.6)

Overall, no group differences or group by time interactions were observed in the hemodynamic responses to 2DG (data not shown). However, diastolic blood pressure did decrease over time, producing a compensatory (Goldstein et al. 1992) increase in heart rate and resulting in a significant time effect for these two variables (F=19.73; df=3,26; P<0.01 and F=8.58; df=3,26; P<0.01).

Plasma NE and DHPG levels in patients with schizophrenia correlated significantly at the baseline (r_s=0.73; df=13; P=0.002) and at 20 min (r_s=0.67; df=13; P=0.008), 40 min (r_s=0.80; df=13; P<0.001) and 60 min (r_s=0.85; df=13; P<0.001). In controls, NE and DHPG levels significantly correlated at the baseline (r_s=0.54; df=11; P=0.05), but not at any other time point (P>0.27). In patients with schizophrenia, plasma NE levels correlated with those of glucose at 20-min (r_s=0.62; df=13; P=0.01), 40-min (r_s=0.63; df=13; P=0.01) and 60-min (r_s=0.69; df=13; P=0.004) time points, but not at the baseline (r_s=0.36; df=13; P=0.19). No NE–glucose relationships were observed in healthy controls at any of the time points (P>0.25).

Discussion

To our knowledge, this is the first study to integrate noradrenergic and glucoregulatory data in patients with schizophrenia. The major finding of this study was that patients with schizophrenia had significantly greater 2DG-induced plasma NE and glucose levels than healthy control subjects. Although neuroglucopenia induced by administration of 2DG (which in this study uncovered a NE-related glucoregulatory dysfunction) is not itself a physiological phenomenon, we believe that our results may have physiological significance in patients with schizophrenia because neuroglucopenia normally induced by insulin has physiological effects similar to those produced by 2DG.

The NE data are consistent with prior reports of sympathetic abnormalities in schizophrenia (Stein and Wise 1971; Lake et al. 1980; Naber et al. 1980; Glazer et al. 1987; Bird et al. 1979a), including amplified NE response to various challenges, i.e., cold pressor, noise and mental arithmetic (Albus et al. 1982). Simultaneous

measurements of NE, epinephrine and DHPG plasma levels employed in this study provided an opportunity to explore potential group differences in the mechanisms responsible for 2DG-induced plasma NE elevations. Plasma levels of any endogenous biochemical represent the ratio of the rate of release of the substance into the bloodstream (spillover) and clearance of the substance from the bloodstream. Assuming that plasma clearance of NE was not decreased during the 2DG glucoprivation, the increments of NE must have been secondary to an increase in spillover, which is determined by the rate of release from the sympathetic nerves, the adrenal medulla or a combination of both.

Studies of 2DG in healthy volunteers have attributed the 2DG-induced NE elevations mainly to the adrenomedullary rather than sympathoneural secretion since these NE elevations were associated with no concurrent increases in DHPG (actually, significant decreases were reported; Breier 1989; Goldstein et al. 1992; Breier et al. 1992). This is because sympathoneural (but not adrenomedullary) stimulation concurrently increases plasma NE and DHPG levels due to increased reuptake of the released NE (Goldstein 1995).

In the present study, plasma NE responses did and plasma epinephrine responses did not differentiate the schizophrenic and control groups. However, DHPG levels increased in the patients and decreased in controls, and there was a positive relationship between NE and DHPG concentrations across schizophrenics; whereas, there was none for the controls. These findings fit with the notion that, among schizophrenic patients, high NE levels resulted from increased sympathoneural release (and reuptake) of NE. In contrast, lower NE responses in controls, decreases in DHPG and the lack of relationship between NE and DHPG levels could be explained by mainly adrenomedullary secretion of NE (Goldstein et al. 1992).

It is of interest that glucose effects were in the same direction as those for NE, i.e., patients with schizophrenia had significantly greater 2DG-induced plasma levels of glucose. While it is tempting to suggest that the observed group differences reflect the impact of schizophrenia neuropathology on the neurocircuitry modulating plasma glucose concentrations (Mukherjee et al. 1996; Ryan et al. 2003), other explanations are also possible.

One potential cause may be that schizophrenia subjects are less physically fit (Brown et al. 1999) or have grater abdominal/intramuscular adiposity (Ryan and Thakore 2002). Both conditions are predictably associated with more insulin resistance leading to higher stimulated plasma glucose and insulin levels (Stear 2003). Higher plasma insulin, in turn, will potentially increase noradrenergic activity resulting in higher NE levels (Baron et al. 1994) and could be the basis of the significant correlation between NE and glucose concentrations in the schizophrenia group.

However, the significant NE–glucose relationship raises a possibility that NE elevations produced by some atypical APDs (e.g., clozapine; Elman et al. 1999a) or by environmental stress may eventually lead by their chronic nature to impaired glucose tolerance. This link is also apparent in other syndromes associated with NE excess, e.g., pheochromocytoma (Skyler 2000) and may involve several peripheral NE's effects including: (1) enhancement of hepatic glucose output (Brodows et al. 1975; Smythe et al. 1989); (2) interference with the normal feedback control exerted by circulating glucose on pancreatic islets secreting insulin and glucagon (Havel et al. 1988); (3) diminution of insulin receptors' sensitivity (Walters et al. 1997); (4) suppressive action on insulin secretion (Matsunaga et al. 1989); and (5) reduction of glucose uptake by skeletal muscles due to NE-induced vasoconstriction (Esler et al. 2001).

Glucose responses in the patients' group may have been influenced also by the use of typical APDs. Indeed, some (Ryan and Thakore 2002; Lindenmayer et al. 2003), but not all (Mukherjee et al. 1989), reports suggest that these agents may contribute to glucose intolerance. Note, however, that it is unlikely that APDs enhanced NE responses to 2DG; if anything, they tend to have a dampening effect on noradrenergic activity (Egan and Hyde 2000). Nonetheless, assessment of the glucoregulatory and noradrenergic systems using 2DG and other metabolic challenge paradigms in APD-free schizophrenic patients would be an important consideration for future research.

A few additional caveats should be considered in interpreting our data. First, the present design cannot rule out that 2DG induced different degrees of central and peripheral glucoprivation in patients and in the control group. Several factors determine the extent of 2DG-induced glucoprivation, other than activation of glucose counterregulatory systems. Probably the most important is the 2DG transport into cells. Like naturally occurring glucose, 2DG undergoes facilitated diffusion into cells by glucose transporters (Horton et al. 1973). The reduced insulin sensitivity that has been proposed to exist in patients with schizophrenia (reviewed in Dwyer et al. 2001), along with the associated reduction in the number and/or activity of glucose transporter proteins, argue against enhancement of intracellular 2DG transport as a basis for exaggerated catecholamine responses in the schizophrenia group. Less is, however, known about possible differences in the enzymes of intracellular phosphorylation (e.g., hexokinase, glucokinase and others). These and other factors that were not a part of the present study design (e.g., glucagon, growth hormone and C-peptide along with changes in gene expression or protein changes) may need to be assessed in future studies. Second, this study assessed only acute 2DG responses (i.e., approximately 50% of the NE elevation, and more than 50% of the glucose elevation was undetermined in this acute study), and longer study periods may have yielded different results. Third, mostly men participated in the experiment and results may not be easily extrapolated to women. Fourth, the subjects' fasting status was not confirmed in study participants, and non-compliance with the fasting requirement might have influenced the results.

Lastly, these findings should be considered preliminary pending replication with a larger sample.

In conclusion, in patients with schizophrenia, 2DG-induced metabolic perturbation elicited heightened NE and glucose responses. We believe that glucoprivic paradigms may have a heuristic value for future investigation aimed at elucidating the mechanisms underlying noradrenergic and glucoregulatory alterations associated with schizophrenia.

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