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Plasma Insulin, Tryptophan and Serotonin Levels during the Glucose Tolerance Test among Habitually Violent and Impulsive Offenders

M. Virkkunen[a], *S. Närvänen*[b]

[a] Psychiatric Clinic and [b] Clinical Laboratory of Children's Hospital, Helsinki University Central Hospital, Helsinki, Finland

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Abstract. Insulin activity in plasma and the concentrations of tryptophan and serotonin were measured during the glucose tolerance test (GTT) in habitually violent and impulsive male offenders and in psychiatric personnel as controls. Insulin was enhanced in the intermittent explosive disorder; at the same time the concentration of plasma tryptophan and the ratio of tryptophan to large neutral amino acids were on a high level and tryptophan even increased in many cases during GTT. Serotonin values did not differ. Many offenders with enhanced insulin secretion displayed abnormal neuroglycopenic symptoms during GTT.

Introduction

There is growing evidence that habitual violence and impulsivity may be associated with biological factors, although in many countries ethical aspects of research have restrained studies among prisoners sentenced for violent crimes. Low levels of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF), possibly caused by slow serotonin turnover in the brain, have been reported among habitually violent military men [Brown et al., 1979, 1982], impulsive homicidal offenders [Linnoila et al., 1983; Lidberg et al., 1984, 1985] and impulsive arsonists [Virkkunen et al., 1987].

Habitually violent and impulsive offenders also tend to have a low blood glucose nadir in the glucose tolerance test (GTT) [Virkkunen, 1982, 1986a, b; Virkkunen et al., 1987]. This reaction appears to be associated with enhanced insulin secretion [Virkkunen, 1983, 1986a, b]. Habitually violent and impulsive individuals often show both low CSF 5-HIAA and low blood glucose nadir [Virkkunen et al., 1986], or low CSF 5-HIAA and enhanced insulin secretion [Kruesi and Linnoila, 1985]. On the other hand, even mild hypoglycemia in GTT has been found to correlate with valid psychological questionnaire scales of aggression [Bolton, 1976; Benton et al., 1982].

An association between brain serotonin metabolism and insulin secretion has been described in the rat [Fernström and Wurtman, 1971, 1972]. Also in healthy, non-obese, fasting men glucose intake increases via insulin the ratio of tryptophan to other large neutral amino acids (LNAAs) in the plasma, which is thought to enhance brain serotonin synthesis [Martin-Du Pan et al., 1982]. Dietary carbohydrates cause an insulin-induced decrement in the concentration of LNAAs also in the human plasma [Martin-Du Pan et al., 1982], but a relatively smaller decrement in total tryptophan concentration (free + albumin-bound) [Lipsett et al., 1973; Martin-Du Pan et al., 1982]. This is explained by the fact that tryptophan, in contrast to other amino acids, is largely bound to albumin [McMenamy and Oncley, 1958].

The present study was undertaken to elucidate the tryptophan level in the plasma and its ratio to that of LNAAs, as well as the changes in these during GTT among habitually violent and impulsive offenders. Plasma insulin and serotonin were measured at the same time. A working hypothesis, based on the above findings, was that plasma tryptophan and its ratio to plasma LNAA might be low in these subjects.

Materials and Methods

Subjects

Sixteen consecutive admissions of habitually violent and impulsive offenders (with some exceptions given below) were investigated in the Mental Examination Department of the Psychiatric Clinic of the Helsinki University Central Hospital. Each of the subjects had committed at least one severe violent crime. The subjects comprised 6 cases with antisocial personality and 10 with intermittent explosive disorder according to DSM-III [1980] criteria. Those with intermittent explosive disorder under the age of 15 did not fulfill the criteria of antisocial personality. Altogether, 4 of those with antisocial personality and 8 with intermittent explosive disorder had a record of more than one violent crime. All had a history of repeated violence. Acts of violence were usually committed under the influence of alcohol, which was also the case in the present violent crimes. One of the subjects with intermittent explosive disorder had also committed repeated arson. All those with intermittent explosive disorder had had discrete episodes of loss of aggressive impulses, resulting in serious assault or destruction of property. These acts were usually grossly out of proportion to any precipitating psychosocial stressor. All 16 subjects also fulfilled the criteria for borderline personality disorder.

All the subjects had a history of severe alcohol abuse, but according to laboratory tests (AST 20.2 ± 3.0 and ALT 24.3 ± 7.8 U/l 37 °C) and clinical examination none had any evidence of liver disease. Offenders who were mentally retarded (IQ less than 68) or who had a chromosome abnormality (XYY or XXY) were excluded from the study. Also excluded were those who had schizophrenia as well as admissions with no violent crimes or tendencies among persons with an antisocial personality. Eight (50%) of the subjects had displayed self-aggression and had made violent, impulsive attempts at suicide.

The offenders had been in prison and without alcohol for several (average 5) months prior to the oral GTT. This test is a routine for all violent offenders in the department. All offenders were admitted several days (at least 3) prior to the study and received a diet with 48–55% of calories as carbohydrates and 37–38% as fat, which is

Table I. Background variables of habitually violent and impulsive offenders and psychiatric personnel (mean values ± SD)

	Group A (n = 10)	Group B (n = 6)	Group C (n = 12)
Age, years	28.6 ± 12.0	33.0 ± 8.4	33.0 ± 9.1
Weight, kg	77.5 ± 8.3	73.9 ± 23.3	74.2 ± 12.8
Height, cm	181.3 ± 5.4	178.9 ± 4.9	177.3 ± 6.9
Relative body weight, %	93.2 ± 7.8	93.8 ± 13.7	91.8 ± 14.4

Group A: habitually violent and impulsive offenders with intermittent explosive disorder; group B: habitually violent and impulsive offenders with antisocial personality; group C: psychiatric personnel.

Table II. Total tryptophan, LNAA, total tryptophan-to-LNAA ratio and Δ insulin levels in the plasma of habitually violent and impulsive offenders and psychiatric personnel during GTT (mean values ± SD)

	Group A (n = 10)	Group B (n = 6)	Group C (n = 12)	F value	p	Significant post hoc differences at $p < 0.05$	
Tryptophan values (μmol/l)							
0 min	74.0 ± 18.0	50.8 ± 13.5	48.8 ± 17.5	6.045	0.007	A > B	A > C
90 min	80.5 ± 57.2	41.6 ± 10.2	41.7 ± 14.6	4.139	0.028		A > C
LNAA values (μmol/l)							
0 min	542.2 ± 158.0	477.3 ± 99.7	521.0 ± 137.1	0.488	0.620		
90 min	437.1 ± 70.5	360.7 ± 101.5	371.8 ± 105.5	1.722	0.199		
Tryptophan-to-LNAA ratio							
0 min	0.154 ± 0.08	0.107 ± 0.02	0.094 ± 0.02	4.104	0.029		A > C
90 min	0.185 ± 0.11	0.128 ± 0.06	0.109 ± 0.03	2.599	0.094		
Insulin, mU/l							
0 min	9.8 ± 5.8	8.8 ± 7.2	6.9 ± 2.8	0.682	0.516		
Δ 15 min	38.3 ± 38.3	51.6 ± 45.6	31.5 ± 16.3	0.863	0.436		
Δ 30 min	94.7 ± 55.2	50.6 ± 29.6	45.6 ± 19.5	4.651	0.020		A > C
Δ 60 min	71.3 ± 32.8	41.6 ± 14.1	44.0 ± 29.3	2.344	0.119		
Δ 90 min	38.1 ± 25.9	19.0 ± 7.8	26.4 ± 19.4	1.798	0.188		

Group A: habitually violent and impulsive offenders with intermittent explosive disorder; group B: habitually violent and impulsive offenders with antisocial personality; group C: psychiatric personnel.

Δinsulin = Insulin level during test – baseline insulin level (mU/l).

standard in the University Central Hospital. During the preceding period in the prisons, the offenders had a diet with about 50% of calories as carbohydrates and 37–38% as fat and with the same total amount of energy as the hospital diet.

A reference group consisted of 12 healthy men from the personnel of the Psychiatric Clinic of the Helsinki University Central Hospital. They were matched as closely as possible for age and weight with the offenders. None of the controls had problems of aggression or alcohol abuse. They were advised to keep to their normal diet during the 3 days preceding the experiments.

The background variables of the subjects and controls are given in table I. There were no differences in age, weight, length or relative body weight between the groups.

Laboratory Procedures

On the morning of the examination, after overnight fasting, baseline blood samples were drawn from all the participants. They were then given glucose (Glycodyn®) orally at a dose 1 g/kg (4 ml/kg) body weight; the solution was to be ingested as quickly as possible. Blood samples were drawn after 0.25, 0.5, 1, 1.5, 2, 3, 4 and 5 h for blood glucose measurement. Blood glucose was determined by the glucose oxidase method [Hjelm, 1966]. Blood samples for insulin measurement were drawn after 0.25, 0.5, 1 and 1.5 h. Insulin was measured by radioimmunoassay technique using Pharmacia's Phadebas Insulin Test [Wide and Porath, 1966].

Blood samples for amino acid analysis were taken at 0 and 1.5 h. The samples were cooled after which proteins of heparin plasma were precipitated with sulfosalicylic acid, centrifuged and supernatants with internal standards analyzed with the Biotronik Amino Acid Analyzer LC 5000.

Samples for blood serotonin determination were taken at 0, 0.25, 0.5, 1 and 1.5 h. Serotonin was measured by the modified fluorometric method [Närvänen, 1983].

Psychic symptoms such as motor restlessness, difficulties to concentrate, fatigue and irritability were observed and elicited every 15–30 min during the 5-hour GTT.

Statistical Methods

Analyses of variance (ANOVA) were carried out at the University of Helsinki Computing Center. If significant interactions were identified, the post hoc Tukey-Kramer test was used when α was 0.05. Two-way ANOVA was used to determine the effect of study groups and time on insulin, tryptophan, serotonin and LNAA concentration, and on the tryptophan-to-LNAA ratio. A two-tailed t test was also used.

Results

Biochemical Values and Changes during GTT

As seen in table II, the Δ 30-min insulin (30-min insulin – basal insulin) value is higher in group A than in group C, indicating a more abrupt enhancement of insulin secretion in the former. The blood glucose nadirs were low both in group A (43.2 ± 18.0 mg/dl, 2.4 ± 1.0 mmol/l) and in group B (41.4 ± 9.0 mg/dl, 2.3 ± 0.5 mmol/l), but not in group C (55.8 ± 11.0 mg/dl, 3.1 ± 0.6 mmol/l). Owing to the conservative statistical method used and the small groups in the study, however, there were no statistically significant differences.

The 0-min tryptophan level was higher in group A than in groups B or C, and the 90-min tryptophan level higher in group A than in group C. There was a great standard deviation in the 90-min tryptophan levels in group A because in many cases the level still rose markedly during the glucose-induced insulin secretion.

The 0-min serotonin values were 121.3 ± 76.6 µg/l in group A, 88.5 ± 52.4 µg/l in group B, and 103.8 ± 45.4 µg/l in group C. There were no statistical differences between the groups. Changes in plasma serotonin were small after 15, 30, 60 and 90 min and the groups did not differ from each other statistically.

A two-way analysis of variance in Δ insulin values for the effect of time, groups and interaction indicated statistical significance ($F = 3.58$; d.f. = 11, 90; $p < 0.001$). There was a statistically significant main effect of time ($F = 3.13$; d.f. = 9, 100; $p < 0.001$), groups ($F = 2.61$; d.f. = 8, 100; $p < 0.05$) but not time × groups interaction ($F = 1.57$; d.f. = 6, 100; p = NS).

The tryptophan values also showed significance ($F = 5.99$; d.f. = 3, 52; $p < 0.002$) and there was a significant main effect of time ($F = 8.82$; d.f. = 3, 50; $p < 0.001$) but not groups ($F = 0.32$; d.f. = 4, 50; p = NS).

There was statistically significant variance in LNAA values ($F = 6.74$; d.f. = 3, 52; $p < 0.001$). Here the significant main effect was that of groups ($F = 17.1$; d.f. 4, 50; $p < 0.001$) but not of time ($F = 1.54$; d.f. = 3, 50; p = NS).

The tryptophan-to-LNAA ratios also showed significance ($F = 4.70$; d.f. = 3, 52; $p < 0.01$). There was again a significant main effect of time ($F = 6.23$; d.f. = 3, 50; $p < 0.001$) but not of groups ($F = 1.63$; d.f. = 4, 50; p = NS). The variance in plasma serotonin values was statistically nonsignificant ($F = 0.240$; d.f. = 14, 125; p = NS).

Psychic Symptoms during GTT

Altogether 8 (6 with intermittent explosive disorder and 2 with antisocial personality) of 16 violent offenders described motor restlessness, fatigue and difficulties to concentrate. These symptoms appeared on average 97 ± 34 min from the beginning of GTT and lasted 1–2 h. Irritability was reported by 4 offenders at the blood glucose nadir. The above-mentioned 8 subjects with psychic symptoms had a mean increase in insulin secretion of 117.9 ± 56.3 mU/l and those who did not describe symptoms 56.3 ± 17.5 mU/l ($t = 2.77$, d.f. = 1; $p < 0.02$). No controls displayed psychic symptoms during the test.

Discussion

The insulin and glucose values observed during GTT support earlier findings. Δinsulin secretion was enhanced in intermittent explosive disorder, which is in line with previous reports [Virkkunen, 1986a, b], and a tendency to low blood glucose nadir was found both in violent antisocial personality and in intermittent explosive disorder. No significant enhancement of insulin secretion in violent antisocial personality has been observed, except possibly in younger age-groups [Virkkunen, 1983, 1986b]. Also in the present study, there was no difference in Δinsulin secretion between subjects with antisocial personality and controls. The youngest subject (21 years) with very violent antisocial personality, however, displayed a strikingly high maximal Δinsulin secretion (173.9 mU/l).

The results of this study support the notion of abnormal tryptophan/serotonin metabolism among habitually violent and impulsive offenders. The working hypothesis on low total tryptophan and tryptophan-to-LNAA ratio in the plasma was not substantiated, however. Total tryptophan and the total tryptophan-to-LNAA ratio was high in intermittent explosive disorder after an alcohol-free period of 5 months on average, and occurred in association with enhanced insulin secretion. According to Fernström and Wurtman [1971, 1972], this should bring about a high tryptophan uptake by the brain, resulting in high serotonin turnover. There is, however, low CSF 5-HIAA among habitually violent and impulsive people, especially so in intermittent explosive disorder [Brown et al., 1979, 1982; Linnoila et al., 1983; Lidberg et al., 1984, 1985; Virkkunen et al., 1986]. The glucose produced, however, an insulin-induced decrement in the concentration of LNAA, and tryptophan-to-LNAA ratio increased as has been found already earlier among normal humans [Martin-Du Pan et al., 1982].

The level of 5-HIAA in the brain reflects just monoamine oxidase activity and not serotonin release in the synapses [Wolf et al., 1985] and so it can be that in spite of low CSF 5-HIAA among habitually violent and impulsive offenders much tryptophan enters the brain but serotonin is not stored properly in the storage vesicles in the neurons and is released easily to the synapses. Motor restlessness and symptoms of concentration difficulties, which have been found already earlier among habitually violent and impulsive offenders [Virkkunen, 1986a], suit this picture. In animal studies there is clear evidence that serotonergic neurotransmission is connected with locomotor activity [Gerson and Balderssani, 1980]. Hyperactivity happens especially when too much serotonin 'spills over onto functional activity' of serotonin neurons as happens, for instance, when laboratory animals get a monoamine oxidase inhibitor followed by *L*-tryptophan [Grahame-Smith, 1971] or tryptophan followed by reserpin when the last-mentioned medicine diminishes brain serotonin in the storage vesicles [Wolf et al., 1985]. Also at least some depressive patients get manic and disinhibition symptoms in these connections [Goff, 1985]. In normal situations dietary tryptophan does not change the functional activity of serotonin neurons although brain 5-HIAA can increase [Trulson, 1985]. Tryptophan can sometimes even decrease the firing rate of these neurons [Young, 1986].

It is often emphasized that in order to count as true reactive hypoglycemia in GTT, a low blood glucose nadir (< 45 mg/dl or 2.5 mmol/l) [Johnson et al., 1980] must be associated with symptoms which subsequently disappear when the normal blood glucose level is restored [Johnson et al., 1980; Gray, 1986]. In the present study, the mean blood glucose nadirs were below these values as has been found also earlier [Virkkunen, 1982, 1986a, b; Virkkunen et al., 1987]. As many of the habitually violent and impulsive offenders also seemed to get abnormal neuroglycopenic symptoms at the glucose nadir, an observation congruent with earlier findings [Virkkunen, 1986a], true reactive hypoglycemia appears to have existed. There is reason for caution, however, because the symptoms described might in part be ascribable to changes in brain serotonin metabolism caused by enhanced insulin secretion. Therefore hypoglycemia is not necessarily the causative agent, although at least irritability has been associated with hypoglycemia [Bolton, 1976; Benton et al., 1982].

The main metabolic route of tryptophan is by tryptophan 2,3-dioxygenase (tryptophan pyrrolase) in the liver [Badaway, 1986]. Insulin secretion is thought to diminish and diabetes to increase the activity of this enzyme [Bitar and Weiner, 1984; Salter and Pogson, 1985]. Therefore it would indeed appear possible in cases of enhanced insulin secretion to encounter total tryptophan values as high as those found in this study. Conversely, a decrease of total tryptophan has been reported in chronic diabetes in the rat [Grandall and Fernström, 1983] and in ketoacidotic diabetes with poor insulin secretion in man [Curzon et al., 1982]. In the latter case, also levels of tryptophan and 5-HIAA in the CSF were above normal.

Further studies concerning biological aspects and psychic symptoms during GTT among habitually violent and impulsive offenders are needed.

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Matti Virkkunen, MD,
Psychiatric Clinic,
Helsinki University Central Hospital,
Lapinlahdentie,
SF–00180 Helsinki 18 (Finland)