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BRIEF COMMUNICATION

Increased plasma concentrations of the 5-HT precursor amino acid tryptophan and other large neutral amino acids in violent criminals

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ABSTRACT

Background. Aggression has been suggested to be related to abnormal brain 5-HT activity. This amine is synthesized in brain from tryptophan, which is transported through the blood–brain barrier in competition with other amino acids. The relationship between tryptophan and its endogenous amino acid competitors in plasma might thus influence the availability of tryptophan in the brain and consequently brain 5-HT activity.

Methods. Plasma amino acids were determined in 89 offenders who had committed various violent and non-violent crimes and in 14 healthy controls.

Results. Both tryptophan and its competitors were higher in offenders who had committed violent crimes compared both with non-violent offenders and with controls. No difference was, however, seen in the relationship between tryptophan and its competitors.

Conclusions. The results support the contention that violent behaviour is related to biochemical deviations but could not explain a possible decreased brain 5-HT activity.

INTRODUCTION

During the last two decades several groups have been able to demonstrate subnormal concentrations of the 5-HT (5-hydroxytryptamine, serotonin) metabolite 5-HIAA (5-hydroxyindoleacetic acid) in cerebrospinal fluid (CSF) in subjects with various forms of aggressive behaviour (Brown *et al*. 1979, 1982; Linnoila *et al*. 1983; Lidberg *et al*. 1984, 1985; Virkkunen & Närvänen 1987). These low 5-HIAA concentrations have been considered to indicate a reduced activity in 5-HT neurons in the brain.

A low concentration of 5-HIAA in CSF has also been reported in depression (Åsberg *et al*. 1976, 1984; Van Praag & Korf, 1971; Westenberg & Verhoeven, 1988), which is well in line with the indolamine hypothesis (Carlsson *et al*. 1969), which claims that depression is related to a decreased activity in 5-HT neurons.

The neurotransmitter 5-HT is synthesized in brain from the amino acid tryptophan. The tryptophan hydroxylase, which enzyme catalyses the rate-limiting step in the 5-HT synthesis, is normally not saturated (Fernstrom, 1983) and thus, the availability of tryptophan in the brain is expected to influence this synthesis.

To reach the brain, tryptophan has to be transported through the blood–brain barrier. This transport is carrier-mediated and takes place in competition with other endogenous large neutral amino acids (LNAA) (tyrosine, phenylalanine, valine, leucine and isoleucine) which all use the same carrier (Oldendorf, 1975; Fernstrom, 1983; Milner & Wurtman, 1986). Thus, the relationship between tryptophan and its competitors will, at least partly, influence the availability of tryptophan in the brain and subsequently the 5-HT synthesis.

In order to reveal possible alterations in the concentrations of tryptophan and its endogenous amino acid competitors in plasma in conditions of aggressive and violent behaviour,

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we have investigated the plasma concentrations of these amino acids in offenders who had committed various forms of violent and non-violent crimes and for comparison also in healthy controls.

METHOD

Male offenders of various crimes who were consecutively admitted by court as in-patients to the Department of Social and Forensic Psychiatry in Stockholm for forensic psychiatric examination (Lidberg & Belfrage, 1991) and who gave informed consent to participate, were, with the following exceptions, included in the study. Those who were infected with human immunodeficiency virus (HIV) were excluded since low plasma tryptophan concentrations have been reported in HIV-positive subjects (Werner *et al*. 1988). Furthermore, since various pharmacological agents are known to influence plasma amino acid concentrations, all those subjects who were on any pharmacological treatment were also excluded. After these exclusions a total of 89 offenders were included in the study.

By the exclusion of all subjects who were on pharmacological treatment the investigation does not include offenders suffering from psychotic or severe affective disorders. Thus, almost every subject included in the study had a diagnosis of some form of personality disorder.

Each subject who was included in the study was assigned to one of six groups depending on the crime (Table 1) that had caused the court to decide on the forensic psychiatric examination.

Table 1. *Numbers and age of investigated subjects in various crime groups and controls*

Group	*N*	Age years Median (range)
Controls	14	29 (23–57)
Non-violent crime	13	32 (18–44)
Sexual crime; rape excluded	8	36 (20–49)
Rape	12	34 (27–57)
Arson	4	26 (23–28)
Violent crime; homicide/ manslaughter excluded	33	29 (20–51)
Homicide/manslaughter	19	33 (20–46)

No statistically significant difference in age was found between the subjects in any of the crime groups and the control group or the group of non-violent crimes, respectively (Mann–Whitney's *U* test).

For methodological reasons previous criminal records were not considered in this assignation. Fourteen healthy men, (staff at a psychiatric clinic and male medical students) were employed as controls (Table 1).

Blood sampling

The blood sampling from the criminal offenders took place several weeks after the respective offender had been taken into custody, since offenders in Sweden are not admitted to forensic psychiatric examination until after both the criminal investigation and a preliminary trial in court.

Fasting venous blood samples were collected from all offenders at approximately 8 a.m. At that time they had had nothing to eat or drink since the previous evening. During at least a few days before the blood sampling they had been in-patients at the Department of Social and Forensic Psychiatry in Stockholm. As such they had been subjected to uniform conditions of diet and activity.

Blood samples from the healthy controls were also collected in the morning after overnight fasting. A difference in activity prior to the blood sampling between the criminal offenders and the healthy controls must, however, be pointed out. The former had spent the night at the place of the blood sampling while the latter had come there from their homes the same morning.

Biochemical and statistical analyses

The blood samples were immediately centrifuged for 10 min at 5000 ***g***. The plasma samples were frozen at −70 °C until assayed. The concentrations of tryptophan and other LNAAs were determined according to methods previously described (Lindroth & Mopper, 1979; Eriksson *et al*. 1989).

From the data obtained in the LNAA analysis the ratio of tryptophan to the total concentration of LNAAs was calculated for each subject.

Statistical significances in the differences in absolute LNAA concentrations and in tryptophan/ΣLNAA ratios between groups were assessed by Mann–Whitney's *U* test (two-tailed). In a first comparison each crime group was compared with the group of healthy controls. In a second comparison each crime group was compared with the group of non-violent crimes.

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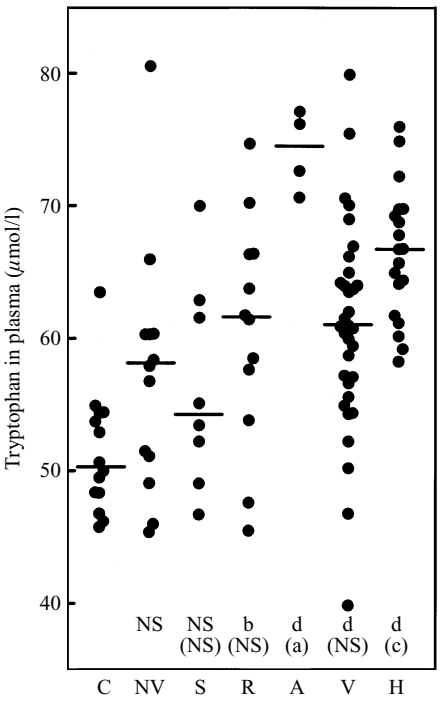

FIG. 1. Concentration of tryptophan in plasma collected from offenders of non-violent crimes (NV) ($N = 13$), sexual crimes, rape excluded (S) ($N = 8$), rape (R) ($N = 12$), arson (A) ($N = 4$), homicide/manslaughter (H) ($N = 19$) and other violent crimes (V) ($N = 33$) and from healthy controls (C) ($N = 14$). Statistical significances were assessed by Mann–Whitney's U test (two-tailed). Statistics, given at the bottom of the figure refer to differences between the respective crime group and the group of healthy controls (without parentheses) and the group of non-violent crimes (in parentheses), respectively. NS = not significant; a = $P < 0{\cdot}05$; b = $P < 0{\cdot}01$; c = $P < 0{\cdot}001$; d = $P < 0{\cdot}0001$.

RESULTS

Fig. 1 gives the concentration of tryptophan in plasma in each subject in each group. The median plasma tryptophan concentration was higher in all crime groups compared with the control group. These differences were statistically significant for rape, arson, homicide/manslaughter and other violent crimes. When compared with the non-violent group significantly higher concentrations of tryptophan were found in the groups of rape, arson and homicide/manslaughter.

The median concentrations of the other LNAAs in each group are demonstrated in Table 2. Most of these amino acids showed higher concentrations in the groups of violent crimes compared with the group of healthy controls. No differences were, however, found between the groups of violent crimes and the non-violent group for any LNAA but tryptophan.

The ratio of tryptophan to the total concentration of LNAAs did not show any statistically significant differences neither in the comparisons between the crime groups and the control group nor in the comparison between the group of non-violent crimes and the other groups (data not shown).

DISCUSSION

Plasma concentrations of tryptophan and other LNAAs were higher in subjects who had committed rape, arson, homicide/manslaughter and other violent crimes compared with the group of healthy controls while the groups of offenders of non-violent crimes and sexual crimes, rape excluded, were found to have LNAA concentrations not significantly different from controls.

These findings indicate a relationship between LNAA levels and violent and aggressive behaviour. This relationship is further strengthened by the finding that the highest LNAA levels were found in the groups of arson and homicide/manslaughter. These crime groups could be expected to include the most violent and aggressive subjects.

The finding of increased plasma concentrations of tryptophan in offenders of violent crimes is well in line with earlier findings of Virkkunen & Närvänen (1987) who also found high concentrations of tryptophan in plasma in patients with intermittent explosive disorder. In contrast, Branchey and co-workers (1984) found decreased concentrations of tryptophan in plasma in alcoholics with aggressive behaviour.

Though consistent with earlier findings of Virkkunen & Närvänen (1987) the present finding of increased concentrations of tryptophan in plasma in offenders of various kinds of violent crimes is, as pointed out by Virkkunen, unexpected and not immediately in line with the findings of low concentrations of 5-HIAA in CSF in impulsive and violent offenders. Furthermore, the finding that the ratio of tryptophan to the total concentration of LNAAs is not altered in the groups of aggressive and violent offenders is inconsistent with the hypothesis that

Table 2. *Plasma concentration of tyrosine, valine, phenylalanine, isoleucine, leucine and the total concentration of large neutral amino acids (LNAA) in subjects referred to various crime groups and in controls*

Amino acid	Controls ($N = 14$)	Crime					
		Non-violent crime ($N = 13$)	Sexual crime; rape excluded ($N = 8$)	Rape ($N = 12$)	Arson ($N = 4$)	Violent crime; homicide/ manslaughter excluded ($N = 33$)	Homicide/ manslaughter ($N = 19$)
	μmol/l median (range)						
Tyrosine	57 (46–121)	61 (42–95)	51 (44–70)	66 (42–110)	69 (55–82)	67 (38–93)	69 (48–85)
Valine	233 (158–264)	239 (177–311)	226 (188–270)	253 (156–420)	260 (208–270)	252* (153–309)	261** (207–379)
Phenylalanine	56 (41–77)	66 (37–92)	63 (47–79)	68** (50–116)	82** (76–95)	64** (47–93)	71*** (56–99)
Isoleucine	70 (45–102)	73 (44–109)	70 (57–94)	85** (66–134)	91* (82–121)	84** (62–127)	88** (61–143)
Leucine	122 (83–202)	138 (94–219)	138 (113–195)	167** (128–254)	183* (134–210)	151** (114–191)	156** (132–219)
ΣLNAA†	586 (418–816)	637 (477–835)	612 (520–758)	695* (568–1105)	761* (628–850)	689** (524–789)	718*** (608–860)

Statistical significances in differences between crime groups and controls, and between the non-violent crime group and the other crime groups, respectively, were assessed by Mann–Whitney's U test (two-tailed). The asterisks in the table refer to differences in the comparison between crime groups and controls. No statistically significant difference was found between subjects in the non-violent crime group and any of the other crime groups.

† Including tryptophan, * = $P < 0{\cdot}05$, ** = $P < 0{\cdot}01$, *** = $P < 0{\cdot}001$.

a possibly decreased 5-HT brain activity might be caused by a decreased availability of tryptophan in the brain.

The present results raise questions about the underlying mechanisms. Plasma concentrations of LNAAs are, at least partly, regulated by adrenergic mechanisms in the periphery: α-adrenergic activity has been demonstrated to cause increased concentration of at least tyrosine in rat plasma (Eriksson & Carlsson, 1982), while β-adrenergic activity causes decreased concentrations in rat plasma of all LNAAs (Eriksson *et al*. 1984). Thus, differences in adrenergic activity might explain the demonstrated differences in plasma amino acid levels.

Actually, a deviant excretion of catecholamines has been demonstrated in subjects with anti-social and violent behaviour. The ratio of noradrenaline to adrenaline in urine has been reported to be four times higher in subjects who had committed severe violent crimes compared with healthy controls (Woodman & Hinton, 1978; Woodman, 1979).

Since noradrenaline is considered to possess a strong α- (and a weak β-) adrenergic activity while adrenaline predominately exerts a β-adrenergic activity (Lefkowitz *et al*. 1990) our finding of high plasma LNAA concentrations could be explained by an altered relationship between noradrenaline and adrenaline in the periphery. Regretfully, the plasma concentrations of these catecholamines were not determined in our investigation.

Furthermore, β-adrenergic activity has been demonstrated to increase the transport of LNAAs through the blood–brain barrier directly, by a mechanism independent of the relationships between the LNAAs in plasma (Eriksson & Carlsson, 1988). If α-adrenergic activity has the opposite effect it is possible that a deviant relationship between α- and β-adrenergic activity also influences the availability of tryptophan in brain.

Needless to say, further studies are warranted to elucidate the biochemical background and the possible clinical relevance of the present observations. In such studies the possible influence of insulin on plasma LNAA concentrations must also be investigated. The secretion of insulin has previously been demonstrated to be deviant in violent and impulsive offenders (Virkkunen & Närvänen, 1987) and insulin is

also known to influence the plasma LNAA pattern (Fernstrom, 1983).

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