Psychological Medicine, 1997, **27**, 473–475.

BRIEF COMMUNICATION

Altered dopamine function in pathological gambling

C. BERGH,[1] T. EKLUND, P. SÖDERSTEN AND C. NORDIN

From the Department of Clinical Neuroscience and Family Medicine, Division of Applied Neuroendocrinology and the Division of Psychiatry, Karolinska Institute, Huddinge, Sweden

ABSTRACT

Background. The possibility that monoaminergic neurotransmission is altered in pathological gambling was examined.

Methods. Monoamines and their metabolites were measured in CSF obtained at level L4–5 from ten pathological gamblers and seven controls.

Results. A decrease in dopamine and an increase in 3,4-dihydroxyphenylacetic acid and homovanilic acid was found. Noradrenaline and its metabolite 3-methoxy-4-hydroxyphenylglycol was also increased but 5-hydroxytryptamine and 5-hydroxyindoleacetic acid were unchanged.

Conclusion. It is suggested that the function of the dopaminergic system, possibly mediating positive and negative reward, and the noradrenergic system, possibly mediating selective attention, is changed in pathological gambling.

INTRODUCTION

Pathological gambling is associated not only with severe psychosocial decay but also with drug and alcohol abuse, depression, anxiety, an altered state of consciousness and deficits of impulse control (American Psychiatric Association, 1987; Bergh & Kühlhorn, 1994*a*, *b*; Roy *et al*. 1988, 1989). Although 5-hydroxytryptamine (5-HT), measured by the concentration of its metabolite 5-hydroxyindole-acetic acid (5-HIAA) in the CSF, plays a role in disorders of impulse control (Mehlman *et al*. 1994), the concentration of 5-HIAA is unchanged in the CSF of pathological gamblers (Roy *et al*. 1988, 1989). The concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), the metabolite of noradrenaline (NA), however, is increased in the CSF (Roy *et al*. 1988, 1989).

Pathological gamblers show signs of arousal and experience alterations in the sense of reward (Bergh & Kühlhorn, 1994*a*, *b*). We speculated that this indicates an altered dopamine function in the brain and tested this hypothesis in the present experiment.

[1] Address for correspondence: Dr C. Bergh, Department of Clinical Neuroscience and Family Medicine, Division of Applied Neuroendocrinology, Karolinska Institute, Novum, S-141 57 Huddinge, Sweden.

METHOD

Twenty-one pathological gamblers, meeting the DSM-III-R criteria (American Psychiatric Association, 1987) and described in detail in the previous studies (Bergh & Kühlhorn, 1994*a*, *b*), were asked to participate. Ten males agreed to the lumbar puncture. Two females were excluded and nine patients were unwilling to rest and fast for 8 h in the hospital, a procedure that preceded the lumbar puncture. There were no other differences between the patients that participated and those that did not. Seven male volunteers participated as controls. They were found healthy in conventional medical and laboratory tests. There was no difference in (mean ± S.D.) age (42·4 ± 8·8 *v.* 38·1 ± 6·1 years), height (181·6 ± 9·2 *v.* 181·9 ± 4·3 cm) or weight (79·1 ± 17·9 *v.* 72·3 ± 6·4 kg) between gamblers and controls. When asked all subjects said they

Table 1. *Mean ± S.D. concentrations of monoamines and metabolites (nmol/l) in the CSF of ten pathological gamblers and seven controls*

	Gamblers	Controls
DA	22·1 ± 6·3*	34·3 ± 7·8
DOPAC	117·0 ± 19·6*	77·1 ± 11·3
HVA	477·1 ± 63·1*	297·6 ± 60·0
DOPAC/DA	5·7 ± 2·0*	2·4 ± 0·7
HVA/DA	23·0 ± 6·8*	8·9 ± 2·1
NA	128·8 ± 30·0*	85·7 ± 19·4
MHPG	55·4 ± 12·6*	37·0 ± 8·9
MHPG/NA	0·5 ± 0·2	0·5 ± 0·2
5-HT	4·8 ± 1·2	5·3 ± 1·1
5-HIAA	309·0 ± 41·8	326·7 ± 50·8
5-HIAA/5-HT	69·2 ± 24·4	65·3 ± 22·6

* $P < 0{\cdot}01$.

had not consumed alcohol within the last 7 days before the experiment.

Lumbar puncture was performed at the L 4–5 level at 08.00 a.m. after at least 8 h of fasting and bedrest. With the subject in a sitting position, three consecutive 6 ml samples of CSF were withdrawn using a disposable needle ($70 \times 0{\cdot}7$ mm). Since there is a lumbar cul-de-sac with reduced or stagnated CSF circulation (Milhorat & Hammock, 1983), assays were performed on the third fraction. Dopamine (DA) and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA), NA, MHPG, 5-HT and 5-HIAA were determined with HPLC-electrochemical detection as described by Bednar *et al.* (1992). The results were compared using unpaired *t* tests.

All patients gave their informed consent and the study was approved by the Ethics committee of the Karolinska Institute.

RESULTS

Table 1 shows that the concentration of DA was decreased and that of DOPAC and HVA was increased in the CSF of the pathological gamblers. Consequently, the ratio between DOPAC or HVA and DA was markedly increased. Also the concentration of NA and MHPG was increased while the ratio between MHPG and NA was unchanged. There was no difference in the concentration of 5-HT or 5-HIAA in the CSF between gamblers and controls.

DISCUSSION

The decrease in the concentration of DA and the increase in DOPAC and HVA in the CSF of pathological gamblers suggests a role of DA in the psychopathology of this disorder. As a consequence, the DOPAC/DA or HVA/DA ratio, i.e. measures of DA release (Cooper *et al.* 1991), was markedly increased. Although differences in enzymatic activity cannot be excluded, this suggests increased release of DA in the brain of pathological gamblers because turnover of DA in the CSF mirrors turnover in the brain (Hutson *et al.* 1984). Some symptoms of pathological gambling such as increased risk-taking and the experience of positive reward (Bergh & Kühlhorn, 1994*a*) indicate an increased level of arousal, which may be a reflection of enhanced activity in ascending mesocorticolimbic DA-systems (Le Moal & Simon, 1991). However, recent evidence suggests that the ascending DA-systems are concerned with negative reward as well. Thus, the behavioural syndrome of opiate withdrawal is mediated by DA D2 receptors in the shell region of the nucleus accumbens (Harris & Aston-Jones, 1994; Besson & Louilot, 1995). It is an interesting possibility that such a DA-mechanism may be related to the behavioural and cognitive signs of withdrawal from gambling in pathological gamblers (Bergh & Kühlhorn, 1994*b*).

Before it is accepted that the present results on DA function are related to pathological gambling it must be pointed out that alcohol abuse is common among pathological gamblers (Bergh & Kühlhorn, 1994*a*, *b*). Alcohol affects DA function in man (Tiihonen *et al.* 1995) and is well known to stimulate release of DA in the brain of animals (Gil *et al.* 1992). However, chronic alcohol administration is less effective than acute administration (Kim *et al.* 1994) and the effect of chronic administration disappears relatively rapid after alcohol withdrawal (Gil *et al.* 1992). Because none of the participants in the present study had consumed alcohol during the 7 days before the lumbar puncture, the possible contribution of the effect of alcohol to the alteration in DA function in the CSF of the pathological gamblers was probably minimal. However, an interactive effect of alcohol and

pathological gambling on DA function is possible.

The present results confirm previous reports of increased levels of MHPG in the CSF of pathological gamblers (Roy *et al*. 1988, 1989) and show in addition an increase in the concentration of NA. Thus, several studies now support a role of NA in pathological gambling. Because of the well-known role of NA in attention (Aston-Jones *et al*. 1994), further studies of this function in pathological gamblers are of interest.

Attempts to relate the increased risk-taking in pathological gamblers to 5-HT neurotransmission (Roy *et al*. 1988, 1989), including the present one, have so far been unsuccessful. However, in other states of deficient impulse control there is clear evidence for a role of 5-HT (Mehlman *et al*. 1994). Obviously, risk-taking does not have a unitary neurochemical correlate. If risk-taking is a form of loss of control over impulse, it follows that impulse control is not merely a simple function of the neural 5-HT systems.

Because of the devastating consequences of pathological gambling (Bergh & Kühlhorn, 1994*b*), further research on its social and biological concomitants is needed. Future studies on the catecholamine systems, known to play roles in some of the behavioural and cognitive functions distorted in pathological gamblers, may be valuable.

The work was supported by the Swedish Commission for Social Research, the Swedish Medical Research Council (7516), the Funds of the Karolinska Institute, the Salus Research Foundation and the Petrus and Augusta Hedlund Foundation.

REFERENCES

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders*, *3rd edn. revised*. American Psychiatric Association: Washington, DC.

Aston-Jones, G., Rajkowski, J., Kubiak, P. & Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience* **14**, 4467–4480.

Bednar, I., Södersten, P. & Qureshi, G. A. (1992). A simple method in monitoring catecholamines, tryptophan, and their metabolites in CSF of rats: a role of dopamine and noradrenaline in food intake. *Journal of Liquid Chromatography* **15**, 3087–3096.

Bergh, C. & Kühlhorn, E. (1994*a*). The development of pathological gambling in Sweden. *Journal of Gambling Studies* **10**, 261–274.

Bergh, C. & Kühlhorn, E. (1994*b*). Social, psychological and physical consequences of pathological gambling in Sweden. *Journal of Gambling Studies* **10**, 275–285.

Besson, C. & Louilot, A. (1995). Assymetrical involvement of mesolimbic dopmainergic neurons in affective perception. *Neuroscience Letters* **68**, 963–968.

Cooper, J. R., Bloom, F. E. & Roth, R. H. (1991). *The Biochemical Basis of Neuropharmacology*. Oxford University Press: New York.

Gil, E., Colado, I., Lopez, F., Fernandez-Briera, A., Fernandez-Lopez, A. & Calvo, P. (1992). Effects of chronic treatment with ethanol and withdrawal of ethanol on levels of dopamine, 3,4-dihydroxyphenylacetic acid and homovanillic acid in the striatum of the rat. Influence of benzodiazepines, barbiturates and somatostatin. *Neuropharmacology* **31**, 1151–1156.

Harris, G. C. & Aston-Jones, G. (1994). Involvement of D2 dopamine receptors in the nucleus accumbens in the opiate withdrawal syndrome. *Nature* **371**, 155–157.

Hutson, P. H., Sarna, G. S., Kantamanemi, B. D. & Curzon, G. (1984). Concurrent determination of brain dopamine and 5-hydroxytryptamine in individual freely moving rats using repeated sampling of cerebrospinal fluid. *Journal of Neurochemistry* **43**, 151–159.

Kim, W.-K., Johnson, R. G., Izu, L. T. & Rabin, R. A. (1994). Chronic ethanol exposure inhibits ATP-stimulated but not KCl-stimulated dopamine release in PC 12 cells. *Journal of Pharmacology and Experimental Therapeutics* **270**, 336–341.

Le Moal, M. & Simon, H. (1991). Mesocorticolimbic dopaminergic networks: functional and regulatory roles. *Physiological Reviews* **71**, 155–234.

Mehlman, P. T., Higley, J. D., Faucher, I., Lilly, A. A., Taub, D. M., Vickers, J., Suomi, S. J. & Linnoila, M. (1994). Low CSF 5-HIAA concentrations and severe impaired impulse control in nonhuman primates. *American Journal of Psychiatry* **151**, 1485–1491.

Milhorat, T. H. & Hammock, M. K. (1983). Cerebrospinal fluid as reflection of internal mileu of brain. In *Neurobiology of Cerebrospinal Fluid 2* (ed. J. H. Wood), pp. 122–147. Plenum Press: New York.

Roy, A., Adinoff, B., Roehrich, L., Lamparski, D., Custer, R., Lorenz, V., Barbaccia, M., Guidotti, A., Costa, E. & Linnoila, M. (1988). Pathological gambling. A psychobiological study. *Archives of General Psychiatry* **45**, 369–373.

Roy, A., De Jong, J. & Linnoila, M. (1989). Extraversion in pathological gamblers. Correlates with indexes of noradrenergic function. *Archives of General Psychiatry* **46**, 679–681.

Tiihonen, J., Kuikka, J., Bergström, K., Hakola, P., Karhu, J., Ryynänen, O.-P. & Föhr, J. (1995). Altered striatal dopamine reuptake site densities in habitually violent and non-violent alcoholics. *Nature Medicine* **1**, 654–657.