British Journal of Psychiatry (1992), **160**, 643–646

Blunted Prolactin Responses to *d*-Fenfluramine in Sociopathy

Evidence for Subsensitivity of Central Serotonergic Function

VERONICA O'KEANE, EAMONN MOLONEY, HELEN O'NEILL, ART O'CONNOR, CHARLES SMITH and TIMOTHY G. DINAN

Using a neuroendocrine probe we studied nine male offenders in a forensic hospital, convicted of murder, with a diagnosis of antisocial personality disorder, who had been behaviourally 'quiescent' for varying periods and who had not recently been abusing drugs. Nine healthy age-matched men also participated. All subjects received 30 mg *d*-fenfluramine (*d*-FEN), a 5-HT releasing agent, orally, after an overnight fast, and serial samples for prolactin estimation were taken hourly for five hours. Responses were significantly impaired in the patients, suggesting a subsensitivity of certain 5-HT systems in antisocial personality disorder, regardless of recent or ongoing behavioural disturbance.

Early reports of abnormalities in peripheral markers of serotonin (5-HT) in impulsive and aggressive individuals (Brown *et al*, 1979, 1982; Linnolia *et al*, 1983) have been followed by studies using neuroendocrine challenges (Siever *et al*, 1984; Coccaro *et al*, 1989; Fishbein *et al*, 1989; Moss *et al*, 1990). The latter approach is less invasive than studies of cerebrospinal fluid (CSF) and offers a direct view of central neurotransmitter function.

Serotonin is thought to modulate secretion of prolactin via neuronal projections from brainstem raphe neurons (van de Kar & Bethea, 1982) which probably stimulate the release of a prolactin-releasing factor from the hypothalamus (Shimatsu *et al*, 1984). The rise in plasma prolactin level from the anterior pituitary following challenge with a selective probe is taken as an index of 5-HT responsivity. The racemic mixture of fenfluramine (*d*,*l*-FEN) causes a dose-dependent increase in prolactin in healthy humans (Quattrone *et al*, 1983) which is presumably mediated via the 5-HT pathway, as this response is blocked by the 5-HT antagonists metergoline (Barbieri *et al*, 1983) and cyproheptidine (Lewis & Sherman, 1985). Animal studies, however, indicate that the *d* isomer is more selective for the 5-HT system than the racemic mixture (Garattini *et al*, 1987; Invernizzi *et al*, 1989) and our unpublished preliminary studies of healthy volunteers showed that it is better tolerated and has fewer side-effects.

In order to test the hypothesis that 5-HT function is altered in the DSM–III–R syndrome of antisocial personality disorder (ASP) (American Psychiatric Association, 1987), using the selective 5-HT agent *d*-FEN to stimulate prolactin release, we selected our sample from a long-stay forensic population of violent, recidivist sociopaths whose antisocial activities had culminated in murder. To see if this hypothesised serotonergic abnormality was a 'trait', about half of the sample had been quiescent for some years. Those with a history of substance abuse were now abstinent.

Method

Nine men fulfilling DSM–III–R criteria for ASP took part in this study (mean (s.e.m.) age 28.6 (1.9) years). All gave fully informed written consent. The DSM–III–R criteria for ASP include a history of conduct disorder with onset before age 15 and a pattern of irresponsible and antisocial behaviour. The latter is defined by the individual filling at least four of ten items. As can be seen from Table 1, where subjects are 'scored' on the number of behavioural items present, all our subjects fulfilled many items in excess of those required to make a diagnosis (mean 8 items). All except subject 5 were repeated offenders with previous convictions for crimes of violence. Four had an ongoing pattern of violent behaviour and five were quiescent for a mean of five years (range 2–8 years).

Subjects 1–5 had been found 'guilty but insane' and ordered by the courts to be held in custody at the Central Mental Hospital, Dundrum (the national forensic hospital located in Dublin). Subjects 6–9 were patients attending psychiatric clinics in a prison served by liaison forensic staff and had had brief 'crisis-intervention' admissions to the Central Mental Hospital. Subject 1 had murdered twice. Subjects 6 and 7 were second-degree relatives, were self-mutilators, and were persistently violent. Subject 5 also filled DSM–III–R criteria for sadistic personality disorder and killed himself by hanging, four months after completion of this study. Subjects 1, 2 and 3 were exemplary patients and spent most of their very structured days facilitating the running of the unit.

Although six of the experimental group had a history of alcohol abuse, the minimum period of abstinence was one year (mean 4.2 years). There was no history of other substance abuse. All had a history of exposure to

https://doi.org/10.1192/bjp.160.5.643 Published online by Cambridge University Press

Table 1
Patient characteristics

Subject number	Age: years	Years in custody	Alcohol abuse	Behaviourally disturbed	ASP 'score' (DSM-III-R)	Prolactin response: mU/l
1	38	13	–	–	7	60
2	35	8	+	–	9	105
3	28	5	+	–	7	0
4	27	2	+	–	8	0
5	24	2	–	–	7	100
6	28	3	+	+	9	0
7	21	2	+	+	9	80
8	33	1	+	+	8	150
9	24	2	–	+	7	0

psychotropic medication but had been drug-free for a mean of 2.1 years (range 4 months to 10 years). None had a history of major depression, brain damage or psychosis.

The control group consisted of nine age-matched (mean 29.8 (1.7) years) healthy men working in St James's Hospital either as doctors or in paramedical disciplines. They had no personal history of any psychiatric disorder, and neither did their first-degree relatives; they all drank alcohol socially. All volunteers were of normal weight and were physically healthy as determined by physical examination and routine laboratory tests.

Subjects presented at 8.30 a.m. having fasted from midnight. They relaxed for 15 minutes after insertion of a cannula in a forearm vein. The cannula was sealed with a rubber bung and heparinised to keep the line patent. Plasma samples were then taken by vacutainer for prolactin estimation at −15 and 0 minutes and thereafter hourly for five hours. At 0 minutes, 30 mg *d*-FEN was administered. Volunteers were supine throughout, and were served a standard light meal at noon.

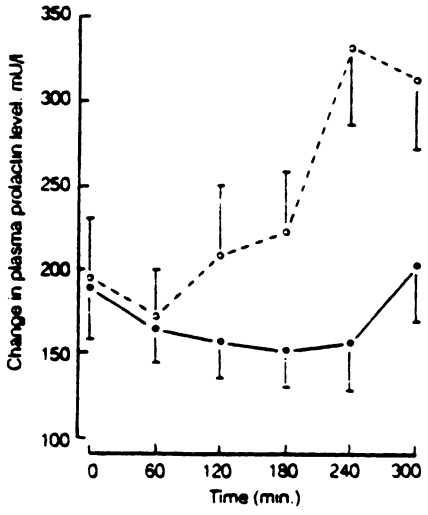

Fig. 1 Plasma prolactin responses over time, following the administration of 30 mg *d*-fenfluramine, in nine patients with antisocial personality disorder (●—●) and nine healthy controls (○----○). Results are expressed as group means, with error bars showing s.e.m.

Prolactin levels were determined blind to subject status by fluoroimmunoassay techniques using a standard commercial kit. This assay has a sensitivity of 1.5 mU/l; an intra-assay precision of 2% and interassay variation of 5.7% (at 110 and 112 mU/l respectively).

Prolactin responses were evaluated as change in prolactin level from baseline (mean of values at −15 and 0 minutes) to maximum. They were taken as zero if the prolactin level dropped below its baseline level. Data were analysed by two-tailed Student's *t*-tests using STATGRAPHICS (Statistical Graphics Corporation, 1987; V 2.7).

Results

The prolactin response curves are shown in Fig. 1. Basal values did not differ between the groups ($t = -1.62$, d.f. = 16, $P = 0.87$). Significantly blunted prolactin responses (maximum minus baseline values) were seen in ASP subjects (55 (19) mU/l, range 0–150) compared with controls (186 (33) mU/l, range 60–280) ($t = -3.44$, d.f. = 16, $P = 0.003$).

In the ASP group there were no differences in responses between those with and without a history of alcohol abuse ($t = -0.05$, d.f. = 7, $P = 0.9$) or between quiescent and disturbed groups ($t = -0.1$, d.f. = 7, $P = 0.9$). As all subjects were aged about 30 years, correlation of age with response was not possible.

Discussion

Serotonergic responsivity is clearly blunted in our ASP sample using *d*-FEN as a probe. The sample size was small because of the exclusion of: those with a recent (within one year) history of substance abuse, which is known to be associated with ASP (Cloninger *et al*, 1978; Haertzen *et al*, 1980); those with histories of major depression, since prolactin responses to *d,l*-FEN are impaired in this disorder (Siever *et al*, 1984; Coccaro *et al*, 1989; Mitchell *et al*, 1990; O'Keane & Dinan, 1991); and those with a history of psychotic episodes. Moreover, we included only those with an

https://doi.org/10.1192/bjp.160.5.643 Published online by Cambridge University Press

extreme ASP syndrome in order to aid the detection of differences with controls. Women were not included because of the difficulty in controlling for the marked fluctuations seen in 5-HT responsivity in healthy women throughout the menstrual cycle (Yatham *et al*, 1989; Dinan *et al*, 1990; O'Keane *et al*, 1991).

These findings compliment those from CSF studies showing a reduction in 5-HT metabolites and probable diminished central 5-HT turnover in violent individuals (Brown *et al*, 1979, 1982; Linnolia *et al*, 1983). Neuroendocrine studies using *d,l*-FEN as a challenge agent demonstrate reduced 5-HT responsivity in impulsive and aggressive patients with a diagnosis of borderline personality disorder (Siever *et al*, 1984). Another group found that prolactin responses to *d,l*-FEN in 20 subjects with different personality disorders were inversely correlated to aggression scores (Coccaro *et al*, 1989). Likewise, Moss *et al* (1990) found that substance abusers with ASP had impaired responses to the 5-HT agonist m-chlorophenylpiperazine, and this blunting was associated with assaultiveness and dysphoria. The taxonomic difficulties presented by ASP substance abusers impede interpretation of these data, because it is not known whether the abnormality results from ASP syndrome, substance abuse or the combined syndrome, as in Cloninger's (1988) type 2 alcoholic. That it may be due to the axis II disorder is indicated by the finding of elevated prolactin response to *d,l*-FEN in substance abusers (Fishbein *et al*, 1989). Those with a recent history of substance abuse were excluded from this study additionally because of the well documented short- and medium-term effects some of these have on neurotransmitter function in the central nervous system (Dackis *et al*, 1984; Ganin & Kleber, 1985). Responses in this study were unaltered by the presence of a history of substance abuse.

Serotonin is thought to modulate aggression by inhibiting behavioural responses to environmental stimuli (Muhlauer, 1985; van Pragg *et al*, 1987). This hypothesis offers a plausible explanation for the frequent observation of remarkably altered behaviour in the extreme syndrome of ASP when environmental conditions are tightly controlled and stimuli limited, as was the case in subjects 1–5 in this study. As prolactin responses were similar in the quiescent group and the acutely disturbed group, the serotonergic subsensitivity seems independent of state. The persistence of this physiological abnormality in spite of environmental manipulation and overt behavioural alteration, implies a certain biological determinism. The results support the idea that it is not serotonergic abnormalities *per se* but the combination of adverse environmental stimuli with 5-HT abnormalities that is necessary for violent behaviour.

This study using a novel serotonergic probe suggests that further endocrine studies of this neurotransmitter system would be of value. Firstly, it needs to be demonstrated that prolactin release by non-serotonergic mechanisms is normal and if so the subtype of serotonin receptors functioning pathologically should be determined.

References

AMERICAN PSYCHIATRIC ASSOCIATION (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). Washington, DC: APA.

BARBIERI, C., MAGNONI, V., RAUHE, W. G., *et al* (1983) Effect of fenfluramine on prolactin secretion in obese patients: evidence for serotonergic regulation of prolactin in man. *Clinical Endocrinology*, **19**, 705–710.

BROWN, G. L., GOODWIN, F. K., BALLENGER, J. C., *et al* (1979) Aggression in humans correlates with cerebrospinal fluid metabolites. *Psychiatric Research*, **1**, 131–139.

———, EBERT, M. H., GOYER, P. F., *et al* (1982) Aggression, suicide and serotonin: relationship to CSF amine metabolites. *American Journal of Psychiatry*, **139**, 741–746.

CLONINGER, C. R. (1988) Neurogenic adaptive mechanisms in alcoholism. *Science*, **236**, 410–416.

———, CHRISTIANSEN, R. C., REICH, J., *et al* (1978) Implications of sex differences in the prevalences of antisocial personality, alcoholism and criminality for familial transmission. *Archives of General Psychiatry*, **35**, 941–951.

COCCARO, E. F., SIEVER, L. J., KLAR, H. M., *et al* (1989) Serotonergic studies in patients with affective and personality disorders. *Archives of General Psychiatry*, **46**, 587–599.

DACKIS, C. H., GOLD, M. S., ESTROFF, H. E., *et al* (1984) Hyperprolactinaemia in cocaine abuse. *Society of Neurosciences Abstracts*, **10**, 1099.

DINAN, T. G., BARRY, S., YATHAM, L. N., *et al* (1990) The reproducibility of the prolactin response to buspirone: relationship to the menstrual cycle. *International Clinical Psychopharmacology*, **5**, 119–123.

FISHBEIN, D. H., LOZOVSKY, D. & JAFFE, J. H. (1989) Impulsivity, aggression and neuroendocrine responses to serotonergic stimulation in substance abusers. *Biological Psychiatry*, **25**, 1049–1066.

GANIN, F. & KLEBER, H. (1985) Neuroendocrine findings in chronic cocaine abusers: a preliminary report. *British Journal of Psychiatry*, **147**, 569–573.

GARATTINI, S., MENNINI, T. & SAMANIN, R. (1987) From fenfluramine racemate to *d*-fenfluramine. *Annals of the New York Academy of Sciences*, **499**, 156–166.

HAERTZEN, C. A., MARTIN, W. E., ROSS, F. E., *et al* (1980) Psychopathic states inventory (PSI): development of a short test for measuring psychopathic states. *International Journal of Addiction*, **15**, 137–146.

INVERNIZZI, R., BERETTERA, C., GARATTINI, S., *et al* (1989) D- and L-isomers of fenfluramine differ markedly in their interaction with brain serotonin and catecholamines in the rat. *European Journal of Pharmacology*, **120**, 9–15.

LEWIS, D. A. & SHERMAN, B. M. (1985) Serotonergic regulation of prolactin and growth hormone secretion in man. *Acta Endocrinologica*, **110**, 152–157.

LINNOLIA, M., VIRKKUNEN, M., SCHEININ, M., *et al* (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations differentiates impulsive from non-impulsive violent behaviour. *Life Sciences*, **33**, 2609–2614.

https://doi.org/10.1192/bjp.160.5.643 Published online by Cambridge University Press

MITCHELL, P., SMYTHE, G., PARKER, G., *et al* (1990) Hormonal responses to fenfluramine in depressive subtypes. *British Journal of Psychiatry*, **157**, 551–557.

MOSS, H. B., YAO, J. K. & PANZAK, G. L. (1990) Serotonergic responsivity and behavioural dimensions in antisocial personality disorder with substance abuse. *Biological Psychiatry*, **28**, 325–338.

MUHLAUER, H. D. (1985) Human aggression and the role of serotonin. *Pharmacopsychiatry*, **18**, 218–221.

O'KEANE, V. & DINAN, T. G. (1991) Prolactin and cortisol responses to *d*-fenfluramine in major depression: evidence for diminished responsibility of central serotonergic function. *American Journal of Psychiatry*, **148**, 1009–1015.

——, O'HANLON, M., WEBB, M., *et al* (1991) *d*-Fenfluramine prolactin responses throughout the menstrual cycle: evidence for an oestrogen-induced alteration. *Clinical Endocrinology*, **34**, 289–292.

QUATTRONE, A., TEDESCHI, G., AGUGLIA, F., *et al* (1983) Prolactin secretion in man: a useful tool to evaluate the activity of drugs on central 5-hydroxytryptaminergic neurones: studies with fenfluramine. *British Journal of Clinical Pharmacology*, **16**, 471–475.

SHIMATSU, A., KATO, Y., OHATA, H., *et al* (1984) Involvement of hypothalamic vasoactive intestinal polypeptide in prolactin secretion induced by serotonin in the rat. *Endocrinology*, **97**, 1096.

SIEVER, L. J., MURPHY, D. A., SLATER, S., *et al* (1984) Plasma prolactin changes following fenfluramine in depressed patients compared to controls: an evaluation of central serotonergic responsivity in depression. *Life Sciences*, **34**, 1029–1039.

VAN DE KAR, L. D. & BETHEA, C. L. (1982) Pharmacological evidence that serotonergic stimulation of prolactin release is mediated via the dorsal raphe nucleus. *Neuroendocrinology*, **35**, 225–230.

VAN PRAGG, H. M., KAHN, R. S., ASNIS, G. M., *et al* (1987) Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. *Journal of Affective Disorders*, **13**, 1–8.

YATHAM, L., BARRY, S. & DINAN, T. G. (1989) Serotonin in the psychobiology of premenstrual syndrome. *Lancet*, *i*, 1447–1448.

Veronica O'Keane, MB, MRCPsych, *Lecturer/Senior Registrar, Psychiatric Unit, St James's Hospital, Dublin 8*; Eamonn Moloney, MB, MRCPsych, *Registrar*; Helen O'Neill, MB, MRCPsych, *Registrar*; Art O'Connor, MB, MRCPsych, *Consultant Psychiatrist*; Charles Smith, MB, MRCP, MRCPsych, *Medical Director, Central Mental Hospital, Dundrum, Dublin 14*; *Timothy G. Dinan, MD, MA, MRCPsych, *Senior Lecturer, Trinity College Medical School, St James's Hospital, Dublin 8, Republic of Ireland*

*Correspondence: *Psychiatric Unit, St James's Hospital, Dublin 8, Republic of Ireland*

https://doi.org/10.1192/bjp.160.5.643 Published online by Cambridge University Press