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Correspondence

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Dopamine D_2 receptor occupancy *in vivo* and response to the new antipsychotic risperidone

SIR: All effective antipsychotics block D_2 dopamine receptors with high affinity and this can be demonstrated in functional imaging by high D_2 receptor occupancy (Farde *et al*, 1992). The atypical antipsychotic clozapine is radically different from all other antipsychotics in that clinical response is associated with low D_2 receptor occupancy (Pilowsky *et al*, 1992), suggesting that different therapeutic strategies may be possible for antipsychotics.

Risperidone is a recently licensed atypical antipsychotic, with an unusual pharmacological profile blocking both D_2 and $5HT_2$ receptors (Leysen *et al*, 1993). While the role of $5HT_2$ receptors remains unclear, the *in vivo* occupancy of D_2 receptors is of considerable interest. Risperidone's *in vitro* receptor pharmacology suggests that the drug has high affinity for the D_2 receptor with Ki of 1.12 nm, approximately equal to haloperidol (Leysen *et al*, 1993). However, its behavioural pharmacology is complex and may suggest that *in vivo* the drug does not efficiently bind to D_2 receptors. The conflict between *in vitro* and *in vivo* pharmacology suggests it is of interest to determine what the occupancy is in an *in vivo* patient setting. Nyberg *et al* (1993) claim only 50% occupancy of D_2 receptors, but that was in two volunteers at sub-therapeutic doses (1 mg), making it impossible to infer anything about occupancy in the therapeutic range.

We have recently had the opportunity to assess D_2 occupancy using ^{123}I-IBZM single photon emission computerised tomography (SPECT) in a schizophrenic patient on a clinically relevant regimen of risperidone on a named patient basis.

Case report. D is a 30-year-old man who was admitted to hospital with a relapse of his schizophrenic illness (first episode seven months earlier: i.e. DSM–III–R schizophrenia). He complained of poor sleep, voices talking to him and making comments, and reported alien thoughts inside his mind. He also admitted to having experienced movements of parts of his body which he thought were caused by someone else, and suspected that people from intelligence services were trying to control him and were able to read his thoughts. His behaviour was bizarre, standing outside for long periods at night partially dressed. He has a family history of schizophrenia, in his mother and a maternal cousin. Previous treatment attempts had been made with pimozide up to 12 mg a day but the patient did not comply with that medication. During this admission to hospital, he was treated with risperidone up to 12 mg a day. This led to a notable improvement in his psychotic symptoms, with return of his sleeping patterns and behaviour to normal, insight to his delusional beliefs and no passivity feelings, although on discharge he still experienced occasional minor auditory hallucinations.

He agreed to take part in our research project investigating D_2 dopamine receptor blockade and antipsychotic response with SPECT. His score on the 24-item Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) was 37 on the afternoon he was scanned. He was then on 12 mg of risperidone a day. This dose is in the mid-range according to open phase II trials with risperidone (Livingston *et al*, 1991). He had received 6 mg at 9 a.m. on the scanning day. The Abnormal Involuntary Movements Scale (AIMS; Wojcik *et al*, 1980) score before scanning was 0, and he denied extrapyramidal side-effects (EPS) or subjective feelings of akathisia.

The method of scanning is described in depth elsewhere (Pilowsky *et al*, 1992). Dynamic single slice SPECT was performed using a brain-dedicated SME 810 multidetector SPECT scanner, immediately after the injection of 185 MBq ^{123}I-IBZM. Fourteen serial slices at a level including the head of caudate and putamen were obtained, with an acquisition time of five minutes each. Semi-quantitative analysis of the data was performed. Ratios between the basal ganglia (BG) activity and the frontal cortex (FC) activity during equilibrium (60–80 minutes post-injection) were obtained and averaged to provide an estimate of the saturable component of binding (an *in vivo* approximation to specific binding) of ^{123}I-IBZM to D_2 receptors.

The mean left (L) and right (R) BG/FC ratios obtained for our patient were both equal to 1.24. These values lie

well within our previously reported range of values for schizophrenic patients responding to typical antipsychotics ($n=10$; LBG/FC = 1.29 ± 0.048, RBG/FC = 1.24 ± 0.045), and is clearly lower than those obtained in either non-medicated ($n=20$; LBG/FC = 1.71 ± 0.027, RBG/FC = 1.65 ± 0.024) or clozapine-treated patients ($n=10$; LBG/FC = 1.48 ± 0.038, RBG/FC = 1.49 ± 0.048) (Pilowsky *et al*, 1992, 1993). This suggests a high level of D_2 occupancy with risperidone.

We believe this to be the first example of a D_2 occupancy SPECT study for risperidone in a patient, and indeed in whom there was a definite clinical response. This is of relevance to understanding the drug's mechanism of action as it is difficult to predict its *in vivo* pharmacology from its experimental pharmacology. Our results suggest that in the therapeutic range the drug fully occupies D_2 receptors. However, in classical terms it is an atypical antipsychotic since it is non-cataleptogenic. This supports the catalepsy test as a valuable screen for effective antipsychotics free from such side-effects without being hampered by presupposition about the mechanisms of action of a drug. Farde *et al* (1992) showed a threshold of D_2 receptor occupancy of about 80% for the development of EPS. The occupancy of risperidone in this case was certainly higher but this patient was free from any side-effects.

The mechanism of this cannot be determined as yet, but clearly it is worth investigating the possibility that $5HT_2$ blockade protects against the provocation of EPS induced by high D_2 occupancy. The role of $5HT_2$ blockade in this drug's action requires full clarification.

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R. W. KERWIN
G. F. BUSATTO
L. S. PILOWSKY

Institute of Psychiatry
De Crespigny Park
Denmark Hill
London SE5 8AF

P. J. ELL
D. C. COSTA

Institute of Nuclear Medicine
University College and Middlesex School of Medicine
London

N. P. L. G. VERHOEFF

Amsterdam Medical Centre and Cygne b.v.
Eidhoven University
The Netherlands

Alcoholics with eating disorders

SIR: Higuchi *et al* (*Journal*, March 1993, **162**, 403–406) conclude that there is an association between eating disorder and alcohol abuse in women, but not in men. It would be dangerous to assume that the two conditions never co-exist in men and I would like to illustrate this by describing a case seen on our unit.

The eating disorder and alcohol abuse seem to have developed concurrently when he was aged 18, but whereas the patient had received treatment on a number of occasions of his alcohol problem, his eating disorder had gone unrecognised for many years.

Case report. C, a 43-year-old man, was admitted electively to the regional addiction unit for alcohol detoxification and to the in-patient abstinence group. He had been assessed as an out-patient, and routine blood tests before admission had revealed a potassium concentration of 2.1 mM/l. His general practitioner had prescribed him potassium supplements. He gave a 25-year history of heavy drinking (12 units or more per day) with a 10-year history of alcohol dependence syndrome. On admission he complained of depressed mood, with diurnal variation, initial insomnia and lethargy. He denied any vomiting or diarrhoea and no obvious case could be found for his hypokalemia.

He had a psychiatric history and had been admitted on at least five occasions to his local psychiatric hospital for treatment of depression and alcoholism. There was no other significant medical history.

He was a slim man, looking rather older than his years, with a plethoric complexion and swollen face. He was clinically depressed. Physical examination was essentially normal other than hepatomegaly and poor dental hygiene.