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SHORT COMMUNICATION

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Decreased benzodiazepine receptor binding in panic disorder measured by IOMAZENIL-SPECT

A preliminary report

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Abstract Single photon emission tomography (SPECT) imaging of the central benzodiazepine receptor (BZr) became possible with the newly developed ligand ^{123}I-IOMAZENIL. The BZr binding was investigated in ten patients with panic disorder (PP) compared to ten epileptic patients (EP). Panic patients had lower IOMAZENIL uptake rates in the frontal, occipital and temporal cortex than EP, indicating the involvement of the BZr complex in panic disorder.

Key words Panic disorder · Benzodiazepine receptor Iomazenil · SPECT

Introduction

Several authors have reviewed the possible role of the gamma-aminobutyric acid$_A$ ($GABA_A$) benzodiazepine receptor (BZr) complex in the pathogenesis of anxiety [Norman and Burrows 1986; Teicher 1988; Breier and Paul 1990; Nutt et al. 1990]. New imaging techniques such as positron emission tomography (PET) or single photon emission tomography (SPECT) provide a powerful tool to assess the involvement of BZr binding in anxiety disorders.

Using the iodinated BZ antagonist IOMAZENIL (^{123}I-Ro 16-0154) for SPECT, this study investigated BZr binding in patients with panic disorder.

Patients and methods

Ten patients with panic disorder (PP) with and without agoraphobia according to DSM-III-R (5 males and 5 females; age 32.3 ± 6.6 years) were investigated. None of the patients had a history of neurological diseases, epilepsy, drug or alcohol abuse. Pregnancy was excluded in all female patients and all patients were drug-free for at least 4 weeks. As a reference group ten patients with epilepsy (EP) (5 males and 5 females; age 28.1 ± 4.2 years) without psychiatric disorders were used and all were treated with carbamazepine.

After informed consent all patients received 185 MBq IOMAZENIL intravenously. In order to exclude secret BZ use, BZ concentration was asessed from blood samples taken during the SPECT scan. All patients were BZ-negative. Thyreoidal uptake of unbound ^{123}iodine was blocked by potassium iodide applied orally 1 day before to 6 days after SPECT examination.

The SPECT scans were performed 90–110 min after injection using a double-head rotating gamma camera (PICKER International). A total of 60 views were acquired in a step-and-shooting technique covering the whole 360° angle. Total acquisition time was 25 min. Reconstruction was performed by filtered back projection using a moderately sharp METZ-filter. Irregular regions of interest were drawn three times independently considering the percentile of the isodense line in at least 50% of total activity: The occipital cortex (right and left area one region) and the frontal cortex (right and left area one region) was measured at the level of the third ventricle. The right and left temporal regions were considered separately at the same level as the pons. From these three measurements the average counts per voxel (0.42 × 0.42 × 0.84 cm) were calculated and normalized to the injected counts/body surface according to the formula:

$$\frac{\text{average counts/voxel}}{\text{injected counts/cm}^2 \text{ of body surface}}$$

This formula was developed after different approaches. Following the recommendations of Verhoeff (personal communication), the uptake values were normalized to kg of weight. But because we found more significant correlations between regional uptake and cm^2 of body surface, this formula was calculated. These correlations must be due to distribution effects of IOMAZENIL (Beer and Schubiger, personal communication) because total body measurements showed that IOMAZENIL is not absorbed in the fat tissue (Verhoeff et al. 1993).

In terms of statistical analyses, group comparisons were performed with two-tailed *t*-tests. Alpha-corrections for multiple comparisons were performed by Bonferroni-Holm adjustment (Bauer et al. 1991).

Results

The analyses of different regions of interest in PP and EP showed the highest activity in the occipital and frontal cortex, followed by both temporal regions (Table 1). The

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Table 1 Panic patients (PP) vs epileptic patients (EP)

Region	PP		EP		t^b	P^c
	Mean[a]	SD	Mean[a]	SD		
Occipital	233	29	285	65	2.3	0.03
Frontal	199	25	242	49	2.4	0.04
Temporal right	146	15	190	36	3.7	0.008
Temporal left	137	17	186	42	3.4	0.009

[a] Average counts/voxel divided by injected counts per cm^2
[b] t-test
[c] P-values after Bonferroni-Holm adjustment

comparison revealed lower values in occipital, frontal and both temporal regions (Table 1). The pons, selected as a reference region for unspecific and free binding, had the lowest uptake (PP, 51 ± 13; EP, 58 ± 27; $t = 0.6$ and P = n.s.) in both groups.

Discussion

The most important finding of this study is the lower IOMAZENIL binding in all cortical regions in PP compared to the EP control group. Despite the fact that only a semiquantification is possible in SPECT studies, there is convincing evidence that measured activity corresponds to BZr binding. The distribution of the highest activity in the occipital and frontal cortex, followed by both temporal regions and the lowest uptake in the pons, agrees with BZ-receptor distributions postmortem (Mueller 1987) and with PET studies (Persson et al. 1989). Moreover, displacement experiments in humans (Beer et al. 1990) and primates (Innis et al. 1991) demonstrated that 90–110 min following IOMAZENIL injection, 80–90% of activity corresponds to specific binding.

A disadvantage of this study was the selection of EP as the reference group, but due to legal restrictions investigations in normals have not been possible. Nevertheless, there is striking evidence that the lower values in PP cannot be explained by an increased uptake in EP, because in epilepsy a focal decrease of BZr binding was described in PET and SPECT studies (Savic et al. 1988; Bartenstein et al. 1991).

The use of carbamazepine in epileptic patients should have no major influence on central-BZr binding, because carbamazepine acts primarily with the peripheral type of the BZr (Post et al. 1984); therefore, an up-regulation of BZr binding is unlikely.

Arguments that the lower IOMAZENIL binding in PP might be due to the secret use of BZ can be refuted by the negative results of BZ concentrations in plasma probes during SPECT investigation. Moreover, none of the patients had received BZ treatment during the last weeks before entering the study. The possibility that the lower uptake in PP might be the result of unknown BZ intake during the last years in terms of a receptor down-regulation is unlikely, because in animal experiments BZr binding was decreased only for a few days after BZ cessation (Mueller 1987), or even increased at day 4 before returning to normal levels at day 7 after lorazepam (Miller et al. 1988) or clonazepam administration (Galpern et al. 1991). Correspondingly, we found in a different study (*results will be published separately)* that even after long BZ treatment depressed patients had after 2 weeks of withdrawal similar SPECT values as our EP reference group.

Finally, differences in cortical regions between both groups cannot be attributed to unspecific binding, because the uptake in the pons corresponding to the lowest specific BZr density (Persson et al. 1989) is not different. Despite these methodological limitations this study supports the involvement of BZr complex in panic disorder. Functional subsensitivity (Roy-Byrne et al. 1990) or an altered BZr "set-point" (Nutt et al. 1990) have been suggested as possibly being pathogenical. Therefore, reduced BZr density could be an additional factor in the pathophysiology of panic attacks.

Moreover, lower IOMAZENIL uptake in panic disorder can also be seen in context with animal data, because a decrease of BZr binding was reported after stress experiments (Medina et al. 1983; Weizmann et al. 1989) or as an inherited alteration as in Maudsley reactive rats (Robertson et al. 1978). Therefore, future SPECT studies should focus on examinations after improvement in order to investigate whether reduced BZr binding changes after therapy.

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