

Psychopathological Correlates of Dopaminergic Disturbances in Major Depression

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Abstract. In a recent report, we confirmed the role of dopamine in the pathophysiology of depression by demonstrating a blunted response of growth hormone (GH) to apomorphine, a selective dopaminergic agonist, in endogenous depressive patients. Few data are available on the possible psychopathological correlates of disturbances in the apomorphine test. In this study, we assessed the relationship between GH response to apomorphine and the Minnesota multiphasic personality inventory (MMPI) scales in a sample of 20 major depressive inpatients. The GH response (area under the curve) after apomorphine injection was positively correlated with the social introversion scale scores ($r = 0.56$, $df = 19$, $p < 0.01$) and the anxiety scale scores ($r = 0.45$, $df = 19$, $p = 0.04$). These results suggest dopaminergic overactivity in anxious psychopathology rather than in depressive psychopathology. The relationship between the social introversion scale score and the apomorphine test is in agreement with the dopaminergic hypothesis of schizophrenic disorders.

Introduction

The growth hormone (GH) secretion following injection of apomorphine, a selective dopaminergic agonist, provides an indirect method to assess central dopamine functioning in psychiatric patients. Indeed, the release of anterior pituitary hormones depends on hypothalamic releasing factors, the secretion of which is controlled by neurotransmitters also implicated in mental illnesses [1]. However, few data are available on the possible psychopathological correlates of disturbances in the apomorphine test. In a recent report [2], we confirmed the role of dopamine in the pathophysiology of depression by demonstrating a blunted GH response to apomorphine in endogenous depressive patients. This finding suggested a hyposensitivity of the dopaminergic hypothalamic receptors controlling GH release in major depression. Studies in schizophrenic and schizoaffective patients showed a positive correlation between GH levels following apomorphine and either positive or negative schizophrenic

symptoms [3-5]. A dopaminergic overactivity also seems to be implicated in mania [6-8] and anxiety [9-11] disorders. Nevertheless, all these results about the relationship between apomorphine test and certain aspects of psychopathology remain subject to controversy.

The Minnesota multiphasic personality inventory (MMPI) scales [12] represent the most widely used and best validated measure of psychopathology and personality functioning for psychiatric population.

The aim of the study was therefore to assess the relationship between GH response to apomorphine and MMPI scales in major depressive patients.

Methods

Subjects

The study was performed in 20 DSM-III-R major depressive inpatients, representing consecutive admissions to the Psychiatric Unit of the University Hospital of Liège, Belgium. All patients had a score of at least 20 on the Carroll self-rating scale for depression

Table 1. Pearson's correlation coefficients between GH response to apomorphine and MMPI scale scores

IN	indecision	0.09
L	lie	-0.32
F	rare endorsement	-0.017
K	correction	-0.43
HS	hypochondriasis	-0.38
D	depression	-0.09
HY	hysteria	-0.23
PD	psychopathic deviate	0.008
MF	masculinity-femininity	0.27
PA	paranoia	-0.31
PT	psychasthenia	0.23
SC	schizophrenia	-0.05
MA	hypomania	-0.10
SI	social introversion	0.56*
AT	anxiety	0.46*
ES	ego strength	-0.19

* $p < 0.05$.

[13]. The sample included 14 male and 6 female patients, with ages ranging from 23 to 60 years (mean age \pm SD = 43.05 \pm 9.5).

All patients were free of medical illness as evidenced by history, medical examination, EKG, chest X-ray, EEG and routine laboratory tests. They had also been drug-free for at least 2 weeks prior to the study. Due to the influence of estrogens of GH secretion [14], we included only premenopausal women and the apomorphine test was always performed between the 3rd and the 12th day of the menstrual cycle. Patients with a basal systolic blood pressure less than 100 mm Hg were excluded from the study. Moreover, in order to be included, patients had to present a basal (t_0) GH level of less than 5 ng/ml before the neuroendocrine test [15].

Finally, all patients were fully informed of the study and gave their consent.

Procedures

The apomorphine challenge test was performed in all subjects at bedrest after an overnight fast. At 07.00 h, an indwelling catheter was inserted in a forearm vein. Blood samples of 10 ml were collected every 20 min from 40 min before to 120 min after subcutaneous injection at 08.00 h of 0.5 mg apomorphine diluted in saline to obtain 0.5 ml.

GH was measured with a double antibody radioimmunoassay [16], with intra- and interassay coefficients of variation of respectively 13.3 \pm 4.7 and 14.8 \pm 9.6% and a detection limit of 0.2 ng/ml.

Automated MMPI [17] and Carroll self-rating scale for depression were performed within 2 days of the apomorphine test.

Data Analysis

GH response to apomorphine was assessed by the area under the curve (AUC) situated between injection [t_0] and the last blood sampling ($t_{120\text{min}}$). Pearson's correlation coefficients were used to assess the relationship between MMPI scale scores and GH response to apomorphine.

Results

Table 1 presents Pearson's correlation coefficients between GH responses to apomorphine and MMPI scale scores.

GH response (AUC) after apomorphine injection was positively correlated with the social introversion (SI) scale scores ($r = 0.56$, $df = 19$, $p < 0.01$) and the anxiety scale scores ($r = 0.45$, $df = 19$, $p = 0.04$). No correlation appeared with the Carroll self-rating scale for depression ($r = 0.09$).

Discussion

The results of this study indicate a relationship between dopaminergic activity and scores on the SI and anxiety scale in major depressive patients. We did not observe any relationship between GH levels after apomorphine and the depression as well as the hypomania MMPI scale scores. Moreover, GH response to apomorphine injection was not correlated with the Carroll self-rating scale for depression.

The positive correlation between GH peak after apomorphine challenge and the social introversion scale scores is in agreement with the dopaminergic hypothesis of schizophrenic disorders [18]. The postulate of a dopaminergic overactivity in psychosis is based upon two main observations. Firstly, dopaminergic agonists such as amphetamine appeared to be responsible in large doses of behavioral disturbances resembling symptoms of paranoid schizophrenia. Secondly, the improvement of psychotic symptomatology by neuroleptics has been related to a central dopamine receptor blockade. Some evidence from clinical research suggests a relationship between dopaminergic hyperactivity and positive symptoms of schizophrenia. Meltzer et al. [3] found a positive correlation between GH response to apomorphine injection and psychosis ratings using the schedule for affective disorders and schizophrenia, change version (SADS-C; delusions, hallucinations and thought disorders). Recently, Zemlan et al. [4] published similar results confirming Crow's theory [19] of a relationship between dopamine receptor supersensitivity and a specific cluster of positive symptoms (thought disorder). Negative symptoms are, however, also positively correlated with dopaminergic activity [3], in agreement with our observation. Indeed, major depressive patients with a high score on the social introversion scale tend to exhibit a dopaminergic overactivity on the apomorphine test.

However, this result is in contrast with a recent report by Liebowitz et al. [20] suggesting a dopaminergic hypoactivity in patients with social phobia. Moreover, King et al. [21] showed a positive correlation between cerebrospinal fluid dopamine levels and extraversion in a sample of depressed patients. Our results confirm the involvement of dopaminergic function in patients with symptoms of introversion and suggest further studies to clarify the real mechanism of central DA receptor sensitivity in social introversion.

In our study, the relationship between GH response to apomorphine and anxiety scale scores supports the dopaminergic hyperactivity hypothesis of anxiety disorders. Indeed, several reports suggest that dopamine might be involved in anxiety states. In an animal study, Hjorth et al. [22] demonstrated that the anxiolytic-like action of low doses of apomorphine was related to the dopamine autoreceptor-mediated reduction of central dopaminergic activity. More recently, Hjorth et al. [10] suggested the usefulness of DA-modulating agents like the atypical DA receptor agonist (-)-3-PPP as new anxiolytics. Fadda et al. [23] previously showed the reduction of stress-induced increases in forebrain dopamine systems by benzodiazepines. Furthermore, Roy-Byrne et al. [9] found a higher plasmatic concentration of homovanillic acid (HVA), a dopamine metabolite, in a subgroup of panic disorder patients characterized by a higher level of anxiety and a greater number of panic attacks in the past year. In a sample of major depressive patients, Timsit-Berthier et al. [11] observed a positive correlation between the contingent negative variation (CNV) amplitude and the level of anxiety, suggesting a dopaminergic overactivity in the more anxious depressive patients. Indeed, in agreement with Marczyński's [24] hypothesis, we recently demonstrated a relationship between CNV amplitude and apomorphine test [25]. All these data provide evidence for dopaminergic dysregulation in anxiety disorders and suggest to assess the utility of DA-modulating pharmacological agents in the treatment of anxiety.

The lack of correlation between GH peak after apomorphine and the Carroll self-rating scale for depression suggests that the apomorphine test might be a 'trait' rather than a 'state' marker of depression. Indeed, it has been widely demonstrated with the clonidine test that depressive patients in complete remission still exhibited blunted GH response [26, 27]. It is reasonable to expect similar results with the apomorphine test. However, longitudinal studies on a sample of endogenous depressive patients in the free interval should be performed to confirm this hypothesis.

Finally, we did not find any relationship between GH levels following apomorphine and the MMPI depression and hypomania scales, suggesting that dopamine receptor sensitivity is more related to anxious psychopathology rather than depressive/manic psychopathology.

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