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Psychiatry Research 94 (2000) 9–18

PSYCHIATRY RESEARCH

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Fenfluramine challenge in unipolar depression with and without anger attacks

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Received 10 June 1999; received in revised form 25 January 2000; accepted 1 February 2000

Abstract

We have previously hypothesized that patients with major depression and anger attacks may have a greater central serotonergic dysregulation than depressed patients without such attacks. We wanted to compare the prolactin response to fenfluramine challenge, as an indirect measure of central serotonergic function, in depressed patients with and without anger attacks. We recruited 37 outpatients (22 men and 15 women; mean age: 39.5 ± 10.5) with DSM-III-R major depressive disorder, diagnosed with the SCID-P. Their initial 17-item Hamilton Rating Scale for Depression score was ≥ 16. Patients were classified as either having or not having anger attacks with the Anger Attacks Questionnaire. All patients received a single-blind placebo challenge followed by a fenfluramine challenge (60 mg orally) the next day. Plasma prolactin measurements were obtained with double antibody radioimmunoassay before and after both placebo and fenfluramine challenges, and fenfluramine and norfenfluramine blood levels after each challenge were determined by gas chromatography. Of the 37 study participants, 17 (46%) were classified as having anger attacks. There were no significant differences in age, gender, fenfluramine, or norfenfluramine blood levels between depressed patients with and without anger attacks. Depressed patients with anger attacks showed a significantly blunted prolactin response to fenfluramine challenge compared to patients without anger attacks. As previous studies have shown blunted prolactin responses to fenfluramine in impulsive aggression among patients with personality disorders, our results support our hypothesis that depressed patients with anger attacks may have a relatively greater serotonergic dysregulation than depressed patients without these attacks.

Keywords: Aggression; Depression; Fenfluramine; Prolactin; Serotonin

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0165-1781/00/$ - see front matter
PII: S0165-1781(00)00120-7

1. Introduction

A number of phenomenological studies have demonstrated the marked heterogeneity of unipolar depressive disorders, which can be accompanied by mood states other than depression itself. We have identified a subtype of depression characterized by the presence of irritability and 'anger attacks'. We initially reported a series of illustrative cases in which patients had presented with 'anger attacks', sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, and tightness of the chest which resembled panic attacks but without the predominant symptoms of fear and anxiety (Fava et al., 1990). These anger attacks were experienced by the patients as uncharacteristic of them and inappropriate to the situations in which they had occurred (Fava et al., 1990). Since treatment of these attacks with antidepressants produced in each case marked improvements in behavior, we hypothesized that these attacks were variants of major depressive disorder (Fava et al., 1990). We subsequently developed the Anger Attacks Questionnaire (Fava et al., 1991), a self-rating scale aimed at assessing the presence of anger attacks, and observed that depressed outpatients had significantly higher rates of anger attacks than healthy volunteers with no known psychiatric history (Fava et al., 1991). Two single-site studies on 127 and 164 medication-free outpatients with major depression showed rates of anger attacks of 44% and 39%, respectively (Fava et al., 1993, 1996). A subsequent multi-center study on depressed outpatients found that anger attacks were present in 38% of 94 patients with atypical major depression and in 28% of 74 patients with dysthymia, with an overall rate of anger attacks of 34%, while 0% of 38 normal control subjects reported them (Fava et al., 1997). Therefore, it appears that the prevalence of anger attacks in depressed populations is approximately 30–40%. In a study among 56 depressed outpatients reporting anger attacks, the mean number of attacks/month was 7.4, and the most frequently reported symptoms or behaviors during the attacks were feeling like attacking others, feeling out of control, tachycardia, and hot flashes (Fava et al., 1993). In addition, 63% of these patients reported attacking others physically or verbally during the attacks, and 30% reported throwing or destroying property (Fava et al., 1993).

We then conducted a series of studies to evaluate whether the presence of these anger attacks in patients with unipolar depression was associated with a characteristic psychological profile. No significant age or gender differences were noted between depressed outpatients with and without anger attacks in two different patient samples (Fava et al., 1993, 1996). On the other hand, depressed patients with anger attacks showed significantly higher rates of anxiety (Fava et al., 1993), as well as somatic symptoms and hostility (Fava et al., 1993, 1996), than depressed patients without anger attacks. Finally, a study using a clinician-rated instrument found that depressed patients with anger attacks had significantly higher rates of dependent, avoidant, narcissistic, borderline, and antisocial personality disorders than depressed patients without such attacks (Tedlow et al., 1999).

A pilot study on outpatients with major depression found that depressed patients with anger attacks had a significantly blunted prolactin response to thyrotropin-releasing hormone (TRH) stimulation compared to depressed patients without anger attacks (Rosenbaum et al., 1993). In addition, treatment with the selective serotonin reuptake inhibitor fluoxetine for eight weeks was followed by a significant increase in the prolactin response to TRH among depressed patients with anger attacks, but not among those without anger attacks (Rosenbaum et al., 1993). Given the inhibitory role played by central serotonin (5-HT) neurotransmission in the hypothalamic release of TRH and the stimulating effect of TRH on the release of prolactin from the pituitary gland, these results were interpreted as suggesting that the subset of patients with major depression and anger attacks might have a relatively greater serotonergic dysregulation than depressed patients without such attacks (Rosenbaum et al., 1993).

Fenfluramine is a 5-HT releasing agent and re-uptake inhibitor (McBride et al., 1990), which exists as a racemic mixture (DL) and increases