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Serotonin indices and impulsivity in normal volunteers

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Abstract

Hormonal responses to oral paroxetine were examined in a group of healthy subjects. The calcium response to serotonin (5-hydroxytryptamine, 5HT), mediated by platelet $5HT_{2A}$, was also measured. Paroxetine elicited a cortisol response that was directly correlated with the magnitude of platelet calcium response. The cortisol response was also correlated with the trait of impulsivity. These results suggest that paroxetine may be a useful probe in studies of serotonergic systems.

Keywords: Paroxetine; Cortisol; Calcium

1. Introduction

A large body of literature indicates that disturbances of serotonin (5-hydroxytryptamine, 5HT) function may play a role in major depression, suicidal behavior, and personality traits that are characterized by impulsivity. A number of symposia have focused on the relationship between 5HT and behavior (Eccleston and Doogan, 1988), highlighting the intense interest in this area. There are many approaches to the investigation of serotonin, including receptor binding and autoradiography, neuroendocrine challenge paradigms, and measurement of metabolites.

Observations of 5HT-mediated hormonal responses to 5HT agonists have been frequently reported. In a number of studies, Coccaro and his associates have used the serotonergic drug fenfluramine in a challenge paradigm to assess overall central 5HT function (Coccaro et al., 1989b). Fenfluramine acts to release 5HT and block its reuptake, stimulating the secretion of prolactin (PRL). In a study of subjects with affective and personality disorders, ratings of aggression and impulsiveness were both inversely correlated with peak PRL levels following fenfluramine administration. A blunted PRL response to fenfluramine (O'Keane et al., 1992) was also found in a group of subjects with antisocial personality disorder, a condition associated with

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prominent impulsivity. Other agonists used in this approach include buspirone (Coccaro et al., 1990) for which the PRL response also correlated with impulsive aggression. After administration of meta-chlorophenylpiperazine, blunted PRL correlated inversely with irritability (Coccaro et al., 1989a) and assaultive aggression (Moss et al., 1990) but not with other measures of impulsiveness. A heritable trait of impulsivity was suggested by the finding that first-degree relatives of probands with personality disorder and blunted PRL responses to fenfluramine exhibited an elevated risk of impulsive personality disorder traits (Coccaro et al., 1994).

A significant drawback of previously used challenge agents is a lack of specific pharmacological action. These agents have diverse effects on different receptor populations and can act both presynaptically and postsynaptically. Furthermore, the secretion of PRL appears to be complex, involving a number of receptors including $5HT_{1B}$, $5HT_{C/2}$, $5HT_3$, dopamine D_2, β-adrenergic, and muscarinic M_1 receptors (Levy and Van de Kar, 1992). The presence of these complexities does not detract from the important observations made in the above-reviewed studies. It does, however, limit the inferences that can be drawn from the responses of specific neurotransmitter systems and measures of personality and behavior.

Other indices of 5HT function associated with the trait of impulsivity include measurement of the 5HT metabolite 5-hydroxyindolacetic acid (5HIAA) in cerebrospinal fluid (CSF). Brown et al. (1979, 1982) found an inverse relationship between aggressive, impulsive, and suicidal behavior and CSF 5HIAA in patients with personality disorders. A replication study evaluated similar measures in 12 subjects with borderline personality. Both lifetime aggression and history of suicide attempts correlated with 5HIAA levels.

Recently, techniques that provide a more in-depth examination at the molecular level such as examinations of receptor-mediated responses to 5HT agonists in platelets have allowed direct observation of 5HT receptor function. Platelet $5HT_2$ receptor number and functioning, as reflected by the magnitude of the serotonin augmentation index (SAI: the increase in adenosine-stimulated platelet aggregation with and without 5HT), neither discriminated depressed subjects nor correlated with measured personality traits (McBride et al., 1994). The number of binding sites (B_{max}) was correlated with the potential lethality of the suicide attempt, and suicide attemptors demonstrated a lower SAI/B_{max} ratio than comparison subjects.

Studies comparing the relationship of central and peripheral measures of 5HT function are beginning to emerge. Mann et al. (1992) reported a positive correlation between CSF 5HIAA and the PRL response to fenfluramine, but not platelet $5HT_2$ receptor binding or the SAI. The SAI did correlate with the PRL response to fenfluramine in a group of autistic subjects (McBride et al., 1989).

One of the purposes of the present study was to evaluate paroxetine as a 5HT challenge agent. This compound has the highest affinity among currently available 5HT reuptake inhibitors for the 5HT transporter and insignificant binding to postsynaptic receptors of any class. Paroxetine lacks affinity for other neurotransmitter transporters and has no active metabolites. These properties appeared to provide significant advantages over previously used challenge agents that do not satisfy the need for specificity. The second aim was to study, in the same subject, the relationship between central neuroendocrine response to paroxetine and platelet $5HT_2$-receptor-mediated stimulation of intracellular calcium (Ca^{++}) in response to 5HT (Affolter et al., 1984; Kagaya et al., 1990), a peripheral measure of 5HT function. As part of an effort to establish a normative data base, subjects completed personality trait measurements of impulsivity, hostility, and sensation seeking.

2. Methods

2.1. Subjects

Ten healthy male volunteers with a mean age of 38.9 years (SD = 6.9) were recruited from medical center staff. Subjects provided informed consent and completed a screening interview to assess personal and family psychiatric history. All subjects were free of mental illness, substance abuse, medi-

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