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Normalization of the diminished prolactin response to buspirone in major depression during imipramine treatment

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Key words: Major depression; Prolactin; Buspirone; Imipramine treatment

There is evidence that serotonergic activity may be reduced in the central nervous system of depressed patients. Neuroendocrine challenge paradigms have been used to test this hypothesis. In this study the prolactin (PRL) response to buspirone, a partial 5-HT1A agonist, was assessed in depressed patients and control subjects.

Nine depressed patients (3 men, 6 women) and 22 healthy controls (12 men, 10 women) participated in this study. All patients met DSM-IIIR criteria for major depressive episode. After a 2-week wash-out period the buspirone-induced prolactin test was performed. Through an indwelling catheter blood samples were obtained six times during 90 min for baseline prolactin measures. Then 30 mg of buspirone was given orally and blood samples ware obtained after 30–180 min (every 15 min). Plasma prolactin concentration was determined by radioimmunoassay. In the depressed group the buspirone test was repeated after 14–21 days of treatment (dose: 150–250 mg/day). The PRL values before buspirone ingestion were averaged together to obtain one baseline value. The maximum response was obtained by subtracting the baseline value from the peak value observed after buspirone intake.

The baseline plasma PRL concentration was not significantly different ($P=0.3247$) in depressed patients (3.7 ± 2.1; range: 1.7–8.3 ng/ml) and control subjects (6.0 ± 4.2; range: 1.8–14.6 ng/ml). The PRL response to buspirone was blunted in depressed patients compared to controls. The maximum PRL response was smaller in the former group (3.3 ± 2.7; range: 0.5–9.0 ng/ml) than in the latter (14.1 ± 6.6; range: 2.0–36.9) ($P=0.0057$). This blunted PRL response increased significantly ($P=0.0117$) in the third week of imipramine treatment to values of 8.8 ± 10.2 (range: 3.5–33.7 ng/ml). This changed hormonal response did not differ from that observed in the control group ($P=0.7784$). We also observed a significant increase ($P=0.0251$) of the baseline PRL level in the depressed group in the third week of the imipramine treatment.

Our study shows that the response of prolactin to buspirone is diminished in depressed patients. This blunted hormonal response normalizes during imipramine treatment. Further study is required to delineate the mechanisms responsible for this abnormal response and its normalization. They may be connected with the 5-HT1A receptor.

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The flesinoxan/5-HT1A receptor challenge in major depression

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Key words: Flesinoxan; 5-HT1A agonist; Neuroendocrine probe; Serotonin; Major depression

A dysfunction in central serotonergic neurotransmission, and particularly in the sensitivity of 5-HT1A receptors, has been widely documented in depression. Agonists of 5-HT1A receptors such as buspirone or ipsapirone stimulate various neuroendocrine responses but lack actual serotonergic selectivity or are not available for intravenous use. Recently, we showed that the intravenous injection of flesinoxan, a highly potent and selective 5-HT1A agonist, induced significant and dose-dependent increases in prolactin, ACTH, cortisol, GH, and total neurophysins and a decrease in body temperature (Ansseau et al., 1992). The tolerance of flesinoxan was excellent and associated with a pleasant feeling of relaxation and slight drowsiness without any GI side effects. Moreover, pindolol, a 5-HT1A antagonist, antagonized the prolactin, ACTH, GH, and

temperature responses to flesinoxan (Ansseau et al., 1993a) whereas ritanserin, a 5-HT2 antagonist, antagonized the prolactin and ACTH responses (Ansseau et al., 1993b).

In the present study, we measured hormonal (prolactin, ACTH, cortisol, GH, total neurophysins and AVP neurophysins) and temperature responses to flesinoxan 1 mg in 12 male inpatients meeting DSM-IIIR criteria for major depression. They had been drug-free for at least 3 weeks before the neuroendocrine procedure and were compared to 12 male healthy controls. Hormones were assayed at −30, 0, +15, 30, 60, 90, and 120 min after the injection of flesinoxan. The two groups differed significantly in their prolactin peak responses (mean ± SD): 165.5 ± 166.5 ng/ml in major depressives vs. 407.1 ± 278.1 ng/ml in controls ($F = 5.82$, df = 2,21, $P = 0.025$). However, there was no difference between the two groups in their responses in ACTH, cortisol, GH, total neurophysins. AVP-neurophysins and body temperature. These results confirm the implication of 5-HT1A receptors in the pathophysiology of depression.

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The flesinoxan/5-HT1A receptor challenge and suicidal behavior

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A dysfunction in central serotonergic neurotransmission, and particularly in the sensitivity of 5-HT1A receptors, has been widely documented in depression. Agonists of 5-HT1A receptors such as buspirone or ipsapirone stimulate various neuroendocrine responses but lack actual serotonergic selectivity or are not available for intravenous use. Recently, we showed that the intravenous injection of flesinoxan, a highly potent and selective 5-HT1A agonist, induced significant and dose-dependent increases in prolactin, ACTH, cortisol, GH, and total neurophysins and a decrease in body temperature (Ansseau et al., 1992). The tolerance of flesinoxan was excellent and associated with a pleasant feeling of relaxation and slight drowsiness without any GI side effects. Moreover, pindolol, a 5-HT1A antagonist, antagonized the prolactin, ACTH, GH, and temperature responses to flesinoxan (Ansseau et al., 1993a) whereas ritanserin, a 5-HT2 antagonist, antagonized the prolactin and ACTH responses (Ansseau et al., 1993b).

In the present study, we measured hormonal and body temperature responses to flesinoxan 1 mg in 12 DSM-IIIR major depressive patients (10 M, 2 F) in relationship to suicidal behavior. The patients were subgrouped into suicide attempters (n = 6) and nonattempters (n = 6). The two groups differed significantly in their delta peak cortisol responses (mean ± SD): 12.5 ± 15.6 μg/l in suicide attempters vs. 86.0 ± 65.0 μg/l in nonattempters ($F = 7.0$, df = 2,10, $P = 0.02$), and in their delta temperature responses: 0.11 ± 0.18°C vs. 0.55 ± 0.33°C ($F = 7.9$, df = 2,10, $P = 0.02$). However, no differences existed between the two groups for ACTH, PRL, GH, AVP neurophysins and total neurophysins. These results support the 5-HT1A receptor downregulation hypothesis of suicidal behavior.

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