The Flesinoxan 5-HT1A Receptor Challenge in Major Depression and Suicidal Behavior

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The prevailing neurochemical theory about biological correlates of suicidal behavior focuses on the serotonergic system. In this study, we assessed the cortisol, ACTH, GH, prolactin and temperature responses to flesinoxan, a5-HT1A agonist, in 30 DSM-III-R major depressed inpatients subgrouped into suicide attempters (n = 15) and nonattempters (n = 15). The patients were assessed after a drug-free period of at least 3 weeks. A subsample of 16 patients completed the Buss-Durkee Hostility Inventory as a measure of impulsive aggressive behavior. Mean delta cortisol responses to flesinoxan were significantly lower in the group of depressed patients with a history of suicide attempts than in the group without history of suicidal behavior: for the delta cortisol values 14.5 ± 16.3 µg/l vs 101 ± 94 µg/l ($F = 8.9$, $df = 5.25$, $p = 0.006$). There was also a very significant difference between suicide attempters and nonattempters for the temperature (delta T°) responses to flesinoxan: 0.20 ± 0.24 °C vs 0.60 ± 0.24 °C ($F = 18.1$, $df = 5.25$, $p = 0.0003$). Hormonal and temperature responses to flesinoxan were not correlated with BDHI irritability or assault subscale scores. The results of the present study support the implication of the serotonergic system, particularly 5-HT1A receptors, in the control of self-directed aggressive behavior. Moreover, in depressed patients, serotonergic abnormalities do not appear to be related to aggressive behavior.

In most countries, suicide ranks among the top 10 causes of death for people of all ages and among the 2 or 3 principal causes of death for individuals aged from 15 to 34 years. In fact, suicide appears to be a very significant public health problem. Therefore, prediction and prevention of suicide are priorities in psychiatric research. For many years, studies about suicidal behavior have largely focused on the role of psychosocial factors in the development of autoaggressive behaviors. Risk factors include male gender for suicide and female gender for suicide attempt, increasing age, loneliness, physical illness, history of recent loss, previous suicidal behavior, and hopelessness. However, the most important risk factor seems to be the presence of a psychiatric illness. Indeed, 90 % of suicides are related to a psychiatric disorder, particularly depression, but also alcoholism, schizophrenia, and anxiety disorders (*Weissman*, et al., 1989; *Henriksson*, et al., 1993; *Rudd*, et al., 1993). However, as suicide is a relatively rare event, the application of these factors in a strategy of prediction and prevention of suicidal behavior is rather disappointing. In the last decade, several studies have suggested that suicidal behavior could be in relationship with biological abnormalities, and particularly with serotonergic dysfunctions (*Asberg*, et al., 1987). In this context, the development of a "biological marker" of suicidal behavior could be useful in the clinical assessment of the suicide risk.

As a first step, we conducted a study to validate a "flesinoxan test" as a serotonergic probe in normal volunteers by showing a reliable and dose-dependent release of various hormones. Moreover, in order to confirm the selective serotonergic mechanisms implicated in the hormonal response to flesinoxan, a strategy using various serotonergic antagonists was used. Until now, no reliable serotonergic hormonal probe for i.v. use has been demonstrated, despite various attempts to stimulate prolactin, cortisol, or GH with several postulated serotonergic agonists, such as 5-HTP, fenfluramine, mCPP, or ipsapirone. These challenges lack serotonergic selectivity and/or are not available for i.v. use: oral administration is compromised by low bioavailability and varying pharmacokinetic parameters.

Flesinoxan is a highly potent and selective 5-HT1A agonist. In a double-blind placebo-controlled study, single doses of 0.5 mg and 1 mg were injected over 10 min into 12 healthy male volunteers at 1-week intervals; temperature and hormonal responses (ACTH, cortisol, PRL, GH, total neurophysins, and vasopressin-neurophysins) were measured at times – 30, 0, 15, 30, 60, 90, and 120 min. Flesinoxan induced a significant and dose-dependent increase in ACTH, cortisol, PRL, GH, and total neurophysins and a decrease in body temperature. The tolerance of flesinoxan was excellent and associated with a pleasant feeling of relaxation and a slight drowsiness without significant GI side-effects. Subsequently, these hormonal and temperature responses to flesinoxan were studied with or without pretreatment with ritanserin, a selective 5HT2 antagonist (10 mg p.o.), or with pindolol, a beta-antagonist and 5HT1A antagonist (30 mg p.o.). The volunteers received at 2-week intervals, in double-blind and crossover conditions, either: 1. flesinoxan 1 mg preceded 90 min earlier by placebo; 2. flesinoxan 1 mg preceded by antagonist; 3. placebo i.v. preceded by antagonist; 4. placebo i.v. preceded by placebo. Pindolol significantly antagonized the prolactin ($p < 0.05$), ACTH ($p = 0.01$), GH ($p < 0.01$), and temperature ($p < 0.05$) responses to flesinoxan. Ritanserin significantly antagonized the prolactin ($p = 0.01$) and ACTH ($p < 0.05$) responses to flesinoxan. These results

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show the role of the 5-HT1A mechanisms in the prolactin, ACTH, GH, and temperature response to flesinoxan, and the role of the 5-HT2 mechanisms in the prolactin and ACTH responses to flesinoxan. Flesinoxan thus appears to fulfill all the criteria for an ideal serotonergic neuroendocrine probe.

In a second step, the flesinoxan test was applied in depressed patients with and without suicidal behavior. Suicidal behavior has been associated with a reduction of serotonergic activity. Indeed, several studies have demonstrated a relationship between low concentrations of cerebrospinal fluid 5-hydroxyindolacetic acid (5-HIAA) and a history of suicide attempts. However, CSF measures of the metabolites of serotonin represent presynaptic indices of serotonergic activity. In contrast, neuroendocrine strategy may provide an indirect index of central neurotransmission at the postsynaptic receptor level and test the functional state of neurotransmission systems. Such a strategy has already been applied in depressed patients with a history of suicide attempts, using the 5-HT releaser/reuptake-inhibitor fenfluramine. *Coccaro* et al. (1989) reported a reduced prolactin response to fenfluramine in patients with major affective disorder and/or personality disorder with a past history of suicidal behavior. In 1984, *Meltzer* et al. showed increased cortisol responses to 5-HTP challenge in depressed suicide attempters. The contradiction between these results could be explained by the fact that the serotonergic precursors used in these neuroendocrine studies stimulate different types of receptors. In fact, these challenges are unable to provide information about which types of 5-HT receptors are implicated in suicidal behavior.

In this study, we assessed the cortisol, ACTH, GH, prolactin, and temperature responses to flesinoxan in 30 DMS-III-R major depressed inpatients subgrouped into suicide attempters (n = 15) and nonattempters (n = 15) and compared to normal controls (n = 12). The patients were assessed after a drug-free period of at least 3 weeks. A subsample of 16 patients completed the Buss-Durkee Hostility Inventory as a measure of impulsive aggressive behavior. There was no significant difference between depressed patients and normal controls for hormonal and temperature responses to flesinoxan. However, mean delta cortisol responses to flesinoxan were significantly lower in the group of depressed patients with a history of suicide attempts than in the group without history of suicidal behavior: $14.5 \pm 16.3\ \mu g/l$ vs $101 \pm 94\ \mu g/l$ ($F = 8.9$, $df = 5, 25$, $p = 0.006$). There was also a very significant difference between suicide attempters and nonattempters for the temperature responses to flesinoxan: $0.20 \pm 0.24\ °C$ vs $0.60 \pm 0.24\ °C$ ($F = 18.1$, $df = 5, 25$, $p = 0.0003$). No significant group differences were observed with regard to PRL, GH, or ACTH. Hormonal and temperature responses to flesinoxan were not correlated with BDHI irritability or assault subscale scores.

Conclusion

The results of this study confirm the major role of serotonin, and particularly 5-HT1A receptors, in the control of inward-directed aggressiveness in major depression and suggest that blunted cortisol and temperature responses to flesinoxan could be considered as "biological markers" of suicidal behavior. Moreover, the flesinoxan test, and particularly the temperature response to flesinoxan, is a less invasive method of assessing central serotonergic neurotransmission than CSF 5-HIAA assessment, and it could be very useful in clinical practice in order to predict suicide risk.

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