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Are Women Sensitive to the Acute Anxiolytic Effect of Diazepam?

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Abstract

Objective: Several studies have shown the influence of ovarian hormones on the GABAergic system. As women are naturally exposed to monthly fluctuation of these hormones, it is possible that their response to benzodiazepines also change over the ovarian cycle. Bearing this in mind, this study aimed to evaluate the possible influence of the ovarian cycle of healthy women on the acute effect of diazepam.

Methods: Forty subjectively healthy women were selected and randomly allocated to two different groups, according to their ovarian cycle phase, follicular (6 to 10 days from the first day of the cycle) or luteal (5 to 10 days after detection of urinary LH peak). Both groups completed the Video-Monitored Stroop Color-Word Test (VMSCWT), an experimental model of anxiety, under the influence of diazepam (10 mg) or placebo. Psychological parameters (State-Trait Anxiety Inventory, Self-evaluation of Tension Level, Visual Analogue Mood Scale) and physiological parameters (heart rate and gastrocnemius electromyogram activity) were evaluated throughout the test. All the data obtained were analyzed using analysis of variance (ANOVA) followed by Tukey's test for post hoc comparisons, both at the 5% significance level.

Results: The results showed that, in the follicular phase, women did not respond to the anxiolytic action of diazepam, although a sedative effect was observed; while in the luteal phase, there was no response to either sedative or anxiolytic actions. As a control for the experimental conditions, a group of 18 men was also administered to the VMSCWT. The results confirmed that both the anxiogenic test and the administered drug were working as expected, since diazepam managed to prevent the anxiety induced by the test.

Conclusion: Therefore, the present findings indicate that the ovarian cycle can alter the effects of the acute administration of diazepam, which can vary from no effect to sedation, without going through anxiolysis.

Keywords: Diazepam; Ovarian cycle; Experimentally-induced anxiety; Stroop test; Healthy subjects; Female brain; Sex hormones

Introduction

The ovarian hormones as all steroid hormones are synthesized from cholesterol, and due to its lipophilicity, have easy access to all cells and organs, including the central nervous system (CNS) [1]. At the cerebral level, these hormones influence the function of many nervous cells, playing an important role in coordinating a number of physical and behavioral changes related to reproductive cycle [2]. However, studies are highlighting the critical role that ovarian hormones may have on the organization of non-reproductive behavior, especially in response to stress and anxiety [3-6].

Progesterone, in the corpus luteum, is converted into, among other metabolites, allopregnanolone (3α-hydroxy-5α-pregnan-20-one), which is secreted under stimulation of the luteinizing hormone (LH) and readily crosses the blood brain barrier [3,7,8]. It has been demonstrated that the 3α-hydroxysteroid is a potent anxiolytic, anticonvulsant, sedative/hypnotic and anesthetic, which exerts its effects through allosteric modulation of the gamma-aminobutyric acid (GABA) receptor complex. By binding to $GABA_A$ receptors, allopregnanolone (alloP) increases the binding of benzodiazepines and GABA to neuronal membranes resulting in increases in the influx of Cl^-. Thus, it has been suggested that alloP enhances GABA-mediated inhibition during states of hyperexcitability of the CNS, such as stress or anxiety [9-13].

Estrogens stimulate the hypothalamic-pituitary-adrenal axis (HPA). This can be observed by: 1) the presence of high levels of free cortisol, both in the morning and in the evening, by pregnant women or women receiving high doses of estrogens [14]; 2) the greater responsiveness of the HPA axis in women compared to men [14]; and 3) the acute administration of estradiol to healthy men in a psychosocial stress situation, which results in hyper responsiveness of the HPA axis and norepinephrine [15]. Furthermore, administration of estradiol to ovariectomized mice increases anxiety in situations of potential threat [16].

In addition to all these effects, estrogens and progesterone can change the density of $GABA_A$ receptors in certain brain regions [17-19] and, as a consequence, they may also alter the effects of certain drugs, such as benzodiazepines. Considering that women are naturally exposed to monthly fluctuation of these hormones, it is possible that their response to benzodiazepines also change over the ovarian cycle.

Studies in rodents have demonstrated changes in the sensitivity to the anxiolytic effect of benzodiazepines during the estrous cycle [20-22]. Moreover, short-term exposure (48-72 h) of female rats to high concentrations of alloP (10 mg/kg in sesame oil) results in increased expression of the α_4 subunit of the $GABA_A$ receptor, with subsequent behavioral and pharmacological changes of GABAergic function, represented by increased anxiety and insensitivity to benzodiazepine [23,24] whereas long-term exposure of female rats to pregnancy-induced high concentrations of alloP results in anxiolysis [25].

In women, the response to benzodiazepines also seems to vary along the menstrual cycle. According to a preliminary study by

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