



Changes in neuroactive steroid secretion associated with CO₂-induced panic attacks in normal individuals

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one;
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Summary Neuroactive steroids modulate anxiety in experimental animals and possibly in humans. The secretion of these compounds has been found to be altered in panic disorder (PD), with such alterations having been suggested to be a possible cause or effect of panic symptomatology. Panic-like attacks can be induced in healthy individuals by administration of panicogenic agents or by physical procedures, and we have now measured the plasma concentrations of neuroactive steroids in such individuals before, during, and after panicogenic inhalation of CO₂ in order to investigate whether abnormalities of neuroactive steroid secretion might contribute to the pathogenesis of PD. Fifty-nine psychologically and physically healthy subjects, including 42 women (11 in the follicular phase of the menstrual cycle, 14 in the luteal phase, and 17 taking contraceptive pills) and 17 men, who experienced a panic-like attack on previous exposure to 7% CO₂ were again administered 7% CO₂ for 20 min. Thirty-three of these individuals (responders) again experienced a panic-like attack, whereas the remaining 26 subjects did not (nonresponders). All subjects were examined with the VAS-A and PSL-III-R scales for anxiety and panic symptomatology before and after CO₂ inhalation. The plasma concentrations of progesterone, 3 α ,5 α -tetrahydroprogesterone (3 α ,5 α -THPROG = allopregnanolone), 3 α ,5 α -tetrahydrodesoxycorticosterone (3 α ,5 α -THDOC), dehydroepiandrosterone (DHEA), and cortisol were measured 15 min and immediately before the onset of CO₂ administration as well as immediately, 10, 30, and 50 min after the end of CO₂ inhalation. Neuroactive steroids were measured in the laboratory of Prof. Biggio in Cagliari, Sardinia, Italy. Neurosteroid levels did not change significantly in both

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responders and nonresponders before, during, or after CO₂ inhalation. These data suggest that neuroactive steroid concentrations before, during, or after CO₂ inhalation do not seem to correlate with panic symptomatology during panic-like attacks in subjects not affected by PD, and they therefore do not support the notion that abnormalities in neuroactive steroid secretion are either a cause or an effect of such attacks.

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1. Introduction

Neurosteroids produced in the central nervous system as well as centrally acting neuroactive steroids secreted in the periphery modulate the expression of anxiety in experimental animals (Beaulieu, 1998). These compounds regulate neuronal excitability with rapid, nongenomic effects that are initiated at the cell surface through agonistic or antagonistic interaction with γ -aminobutyric acid type A (GABA_A) receptors inserted in the membrane of glutamatergic neurons of the amygdala and hippocampus (granular cells, pyramidal and pyramidal-like neurons) acting by intracellular membrane diffusion after being produced by these neurons (Wieland et al., 1991; Paul and Purdy, 1992; Patchev et al., 1994; Barbaccia et al., 1996; Brot et al., 1997; Beaulieu, 1998; Concas et al., 1998; Akwa et al., 1999; Rupprecht and Holsboer, 1999; Bitran et al., 2000; Engel and Grant, 2001; Akk et al., 2005; Agis-Balboa et al., 2006, 2007; Pinna et al., 2008; Gartside et al., 2010).

Although neuroactive steroids have been implicated in humans in the response to stress and in certain neurological and psychiatric conditions, such as depression, ethanol withdrawal, and epilepsy, data obtained from individuals with anxiety disorders, including panic disorder (PD), have been inconclusive with regard to a potential pathogenic role for these compounds (Rupprecht and Holsboer, 1999; Barbaccia et al., 2000; Bicikova et al., 2000; Spivak et al., 2000; Semeniuk et al., 2001; Heydari and Le Mellado, 2002; Rupprecht, 2003). Either normal or greater than normal levels of anxiolytic neuroactive steroids, which act as agonists at GABA_A receptors, or reduced levels of neuroactive steroids that act as GABA_A receptor antagonists have been detected in men or women with PD in the periods between panic attacks, whereas no changes in neuroactive steroid secretion were observed in such individuals after clinically successful short- or long-term pharmacological therapy (Bicikova et al., 2000; Strohle et al., 2002; Brambilla et al., 2003, 2004; Pisu and Serra, 2004; Brambilla et al., 2005; Eser et al., 2005). Panic attacks induced in PD patients pharmacologically with pentagastrin, sodium lactate, or cholecystokinin tetrapeptide have been found to be accompanied by no change in neuroactive steroid levels, or by a reduction in the level of neuroactive steroids that act as GABA_A receptor agonists, or an increase in that of those that act as receptor antagonists (Zwanzger et al., 2001; Tait et al., 2002; Strohle et al., 2003; Zwanzger et al., 2003; Eser et al., 2005; Dell'Osso et al., 2009), suggesting that such changes might contribute to panic symptomatology in PD patients. On the other hand, individuals with subthreshold panic-agoraphobic symptomatic spectrum have elevated blood levels of the anxiolytic GABA_A receptor agonist dehydroepiandrosterone (Dell'Osso et al., 2009). Despite data suggestive of a role for neurosteroid secretion in the pathogenesis of PD, it remains

unclear whether altered secretion between or during panic attacks is a cause or consequence of the psychopathology, in the last case possibly acting as a buffer for the anxiety disorder (Rupprecht et al., 2001),

Panic attacks can be induced in apparently normal individuals by acute stimulation with panicogenic substances or by physical panicogenic procedures, possibly as a result of a preexisting elevated anxiety or "anxiety sensitivity" or of specific personality traits such as physical aggressiveness, irritability, somatic anxiety, or stress susceptibility (Perna et al., 1995; Zinbarg et al., 2001; Perna et al., 2003; Coryell, 2004; Battaglia et al., 2007; Schmidt and Zvolensky, 2007; Battaglia et al., 2009; Esquivel et al., 2009; Toru et al., 2010). Increased secretion of 3 α ,5 α -tetrahydrodesoxycorticosterone (3 α ,5 α -THDOC), adrenocorticotrophic hormone, and cortisol was detected in healthy volunteers in association with cholecystokinin tetrapeptide-induced panic attacks, and was suggested to reflect activation of the hypothalamic-pituitary-adrenal axis contributing to termination of the anxiety-stress response through enhancement of GABA_A receptor function (Eser et al., 2005). Given that some apparently normal individuals might develop PD in response to specific life experiences or to stimulation with panicogenic substances, we set out to study the secretory patterns of neuroactive steroids in healthy subjects who developed panic attacks after a previous CO₂ inhalation, in an attempt to determine the possible influence of neurosteroid alterations on predisposition to PD. Our subjects could be considered as predisposed to PD, and therefore to be intermediate between normal subjects and panic patients. Inhalation of CO₂ affects neurosteroid secretion in experimental animals (Barbaccia et al., 1996), and it induces panic attacks in both normal individuals and PD patients when administered at 7% over 20 min or at 35% in a single breath (Gorman et al., 1990; Perna et al., 1995; Coryell, 2004; Battaglia et al., 2007). We administered air containing 7% CO₂ for 20 min to a group of physically and psychologically healthy subjects with no personal or familial history of psychopathologies of any type. Consistent with previous observations, some of the subjects (responders) experienced acute panic symptomatology that was immediately extinguished by interruption of CO₂ inhalation. After a period of 1–11 months, during which the subjects did not experience spontaneous panic attacks, we again administered 7% CO₂ for 20 min to the responders. These subjects were perfectly conscious that the eventual panic attack could be immediately blocked by interrupting CO₂ inhalation, were absolutely not scared by the procedure which had been amply explained to them, accepted the risk of a panic attack knowing by the precedent experience that it was innocuous and was not going to occur spontaneously thereafter. Only a subset of these individuals experienced another panic crisis, which was not more severe than the first one but was severe enough to make some of them to interrupt

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