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The hypothalamic-pituitary-adrenal axis in anxiety and panic

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Abstract

This review article focuses on the differential activation of the hypothalamic-pituitary-adrenal (HPA) axis in generalized anxiety and panic. The results of experimental studies that assayed adrenocorticotrophic hormone, cortisol and prolactin show that real-life panic attacks as well as those induced by selective panicogenic agents, such as lactate and carbon dioxide, do not activate the HPA axis. Accordingly, experiments carried out in two animal models of panic, namely electrical stimulation of the dorsal periaqueductal gray matter of the rat and the escape from the open arm of the elevated T maze, have shown that in neither case stress hormones are increased in the plasma. Also in humans, reported results have shown that neither cortisol nor prolactin levels were increased following simulated public speaking, an experimental task that has been related to panic, in either healthy volunteers or patients with panic disorder diagnosis. Therefore, although the panic attack causes a major sympathetic stimulation, it has little effect on the HPA axis. In contrast, anticipatory or generalized anxiety activates both the HPA and the sympatho-adrenal axes. **Keywords:** stress hormones, generalized anxiety, panic, simulated public speaking, periaqueductal gray matter, elevated T maze.

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Introduction

The concept of stress is based on the observation that different kinds of physical or psychological demands on the organism elicit the same set of bodily changes, the so called General Adaptation Syndrome (GAS) (Selye, 1936; Ursin & Olff, 1993). However, Hans Selye (1974) himself acknowledged that the original name was not the best one: *"...when I introduced the word stress ..., my English was not yet good enough for me to distinguish between the words stress and strain. It was not until several years later that the British Medical Journal called my attention ... that according to Selye stress is its own cause. Actually I should have called my phenomenon the strain reaction and that which causes it 'stress', which would parallel the use of these terms in physics. However, ... biological stress in my sense of the word was so generally accepted in various languages that I could not have redefined it. Hence, I was forced to create a neologism and*

introduce the word stressor; for the causative agent, ... retaining stress for the resulting condition". (Selye, 1974, as cited in Pac k & Palkovits, 2001).

The most characteristic stress response is the release of the adrenocorticotrophic hormone (ACTH) and corticoids (cortisol in humans and cortisone in the rat) into the blood stream as a result of activation of the hypothalamic-pituitary-adrenal (HPA) axis. In addition to the HPA axis, acute stress also activates the sympathetic division of the neurovegetative nervous system as part of the fight/flight reaction, or emergency response, defined by Walter Cannon (1914). As a result, noradrenaline is released from peripheral sympathetic nerve fibers in different tissues, and adrenaline (also some noradrenaline), from the adrenal medulla into the blood stream.

More recently, McEwen has introduced the concept of allostasis, that is, maintaining stability through behavioral change, as a fundamental process through which animals actively adjust to predictable or unpredictable stressors; allostatic load refers to the cumulative cost of allostasis to the organism, with allostatic overload being a state in which pathology can occur (McEwen & Wingfield, 2003).

Stressors may be physical, such as tissue damage or extreme changes in temperature, but may also be psychological. As to the latter, reported results have consistently shown that the HPA axis and sympathetic nervous system are activated by novelty or cues that signal the delivery of punishment or the withholding of an expected reward (frustration), thus generating anticipatory anxiety. The neural circuits that mediate

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the neuroendocrine responses to psychological stressors include the cortical activation of the basolateral nucleus of the amygdala, which in turn activates its central nucleus. The message is then conveyed to hypothalamic neurons by different pathways: a direct one, an indirect one, through the bed nucleus of the *stria terminalis*, and still another one, through brainstem serotonin (5-HT) and catecholamine-containing neurons. Neurons of the hypothalamic paraventricular nucleus secrete the corticotrophic releasing hormone (CRH) into the portal circulation of the pituitary gland. In the anterior pituitary, CRH stimulates ACTH-secreting cells that release ACTH into the blood stream. ACTH acts on the adrenal cortex promoting cortisol release into the blood stream. In addition to ACTH, prolactin is consistently released at the anterior pituitary in stressful conditions (Van der Kar & Blair, 1999).

To test the GAS hypothesis, Miklós Palkovits and coworkers have used five different stressors: immobilization, hemorrhage, cold exposure, pain, or hypoglycemia. With the exception of immobilization stress, these stressors also differed in their intensities. Their results showed marked heterogeneity of neuroendocrine responses to various stressors and that each stressor has a neurochemical “signature.” By examining changes of Fos immunoreactivity in various brain regions upon exposure to different stressors, they also described stressor-specific pathways and circuits. As a result, they have defined stress as a state of threatened homeostasis (physical or perceived threat to homeostasis) that triggers stimulus-specific adaptive compensatory responses. The adaptive response reflects the activation of specific central circuits and is genetically and constitutionally programmed and constantly modulated by environmental factors (Pacák & Palkovits, 2001). This view may help to understand the seeming paradox on panic attacks and the HPA axis that is discussed in the following section.

Defense-related emotions

Anxiety, fear and panic are emotions related to threat. The distinction between anxiety and fear has not always been clear, but the ethoexperimental approach developed by Robert and Caroline Blanchard (Blanchard & Blanchard, 1988) has provided a sound criterion based on the systematic study of animal defensive strategies against predators. From this perspective, anxiety is the emotion related to risk-assessment behavior that is evoked in situations when the danger is uncertain (potential threat); either because the context is novel or because the danger stimulus (e.g., a predator) had been present in the past, but is no longer in the environment. The notion of risk assessment overlaps with that of conflict, which is a cornerstone of anxiety research. In contrast, fear is related to defensive strategies that occur

in response to actual danger that is at a certain distance from the prey (distal threat). In this case, the animal either evades the situation, whenever an escape route is available or becomes tensely immobilized (freezing), when there is no way out. Finally, panic corresponds to the vigorous flight reaction evoked by very close danger (proximal threat), such as an approaching predator or by acute cutaneous pain. Complete immobility also occurs in response to proximal danger, as well as defensive fight, which occurs when flight is impossible. Nevertheless, the latter strategy relates to rage, rather than to panic (see also Gray & McNaughton, 2000, McNaughton & Corr, 2004). Concerning psychopathology, it has been suggested that the same neurobiological processes that regulate anticipatory anxiety are involved in generalized anxiety disorder (GAD); the ones that control fear, in phobic disorders, and those organizing proximal defense, in panic disorder (PD) (Deakin & Graeff, 1991).

According to the DSM IV classification of psychiatric disorders (American Psychiatric Association, 1994), PD is characterized by the occurrence of panic attacks, in which feelings of extreme fear and dread strike unexpectedly and repeatedly, accompanied by intense physiological symptoms. Over time, anticipatory anxiety about having a further attack and avoidance of places where having an attack is embarrassing develop. The extreme form of avoidance is agoraphobia, in which case the person is afraid of leaving home alone. In contrast, the main symptom of GAD is exaggerated worry and tension over every day events and decisions, lasting for at least six months. In addition to the different clinical manifestations, the pharmacological profile of these disorders also differs: GAD is rapidly ameliorated by anxiolytic drugs, PD by chronic administration of antidepressants (Nutt, 2005).

Emotions, either normal or abnormal, are manifested in both psychological (cognitive, affective, behavioral) and physiological (neurovegetative, neuroendocrine) domains. The question that is central to the present article is whether anxiety/GAD and panic/PD differ qualitatively or only quantitatively as to the activation of the HPA axis.

Neuroendocrinology of panic and anxiety

A naturally occurring PA can be considered as a traumatic stressor (McNally & Lukach, 1992). Assuming the GAS hypothesis—there is single stereotyped hormonal response to all kinds of stressors—, it is expected that the HPA axis would be much more activated by a panic attack than by anxiety. Yet, the majority of the reported results indicate that the HPA axis is little affected by PAs. Thus, a review of the literature on stress hormone responses during PAs (Graeff, Garcia-Leal, Del-Ben, & Guimarães, 2005) showed that real-life PAs as well as those induced by selective panicogenic agents, such

as lactate and carbon dioxide, do not activate the HPA axis. Agonists of the colecystokinin receptor B, such as the colecystokinin-4 peptide (CCK-4) and pentagastrin, increase stress hormones regardless of the occurrence of a PA and thus seem to activate the HPA axis directly. The benzodiazepine antagonist flumazenil does not increase stress hormones, but this agent does not reliably induce a PA. Pharmacological agents that increase anxiety in both normal subjects and panic patients, such as yohimbine, 1-(*m*-chlorophenyl) piperazine (mCPP), fenfluramine and caffeine and mCPP consistently raised stress hormone levels.

The above evidence indicates that natural PAs fail to activate the HPA axis, in contrast to anticipatory anxiety. Yet, the HPA axis responsivity to mild stress seems to be normal in children of parents with PD (Battaglia et al., 1997), but in adult PD patients, there is a reduced response to mild stress (Stones, Groome, Perry, Hucklebridge, & Evans, 1999) as well as to a combined dexamethasone-corticotropin-releasing hormone challenge (Schreiber, Lauer, Krumrey, Holsboer, & Krieg, 1996). Therefore, the HPA axis may become progressively desensitized after repeated exposure to PAs (Van Duinen, Schruers, Maes, & Griez, 2006). Another possibility is the uncoupling of the HPA axis and the noradrenergic-hypothalamic-pituitary-adrenal axis, which is always markedly activated during the PA (Coplan et al., 1995). In contrast to PD, both the HPA axis and the sympatho-adrenal axis are activated by anticipatory anxiety (Mason, 1975). In acute anxiety, the activation of the HPA axis is adaptive, since among other things corticoids seem to reduce perceived fear by impairing memory retrieval of emotionally arousing information (Soravia et al., 2006).

Experimental tests of the hypothesis that brain systems involved in PA do not activate the HPA axis have been conducted in animal models of anxiety and in human experimental anxiety trials.

Tests with animal models of anxiety

Since the PAG has been implicated in the PA, electrical or chemical stimulation of this brain structure has been used as an animal model of panic (see Graeff & Zangrossi Jr., 2002). In one of these models, developed by L.C. Schenberg and coworkers, behavioral items evoked by electrical stimulation of the dorsal PAG of the rat, such as freezing, running, galloping, and so on were measured. The most important finding was that PAG-evoked galloping was selectively attenuated by clinically-effective panicolytics, given in a dose-regimen and time-course not far from those of panic therapy. Particularly, galloping was either attenuated or virtually abolished by 21-day administration of the 5-HT reuptake inhibitors clomipramine and fluoxetine. Treatments that are clinically ineffective on PD, such as the acute

administration of these antidepressants and diazepam, or the acute and 10-day administration of buspirone, did not attenuate the PAG-evoked behaviors. In addition, PAG-evoked galloping was selectively facilitated by peripheral injections of pentylentetrazole, a putative panicogen in humans (Schenberg, Bittencourt, Sudre, & Vargas, 2001; Schenberg, Capucho, Vatanabe, & Vargas, 2002; Vargas & Schenberg, 2001). These pharmacological results indicate that galloping induced by DPAG electrical stimulation is a reliable panic model.

Using this model, Schenberg, Dos Reis, Ferreira Póvoa, Tufik and Silva (2008) have examined whether the plasma levels of stress hormones are changed following PAG-evoked behaviors. The obtained results have shown that ACTH and prolactin plasma concentrations remain unaltered following the PAG-evoked defensive reactions. Not even a 5 minute electrical stimulation of the dorsal PAG at the flight threshold intensity significantly changed ACTH plasma level. The activity of the HPA axis has also been assessed in another experimental model that associates flight/escape behavior with PA, the elevated T-maze (for a review of this model see Graeff & Zangrossi, 2002; Pinheiro, Zangrossi, Del-Ben, & Graeff, 2007). As this test also allows the measurement of inhibitory avoidance, it has been possible to draw direct comparisons on the activity of the axis after expression of a PA or a GAD-related defensive response. The elevated T-maze is derived from the elevated plus-maze by sealing the entrance to one of its enclosed arms. As a result, the T-maze consists of three arms of equal dimension (50 x 12 cm) elevated 50 cm from the floor. One of these arms is enclosed by lateral walls (40 cm high) and stands perpendicular to the two opposite open arms. When placed at the end of the enclosed arm, the rat does not see the open arms until it pokes its head beyond the walls of the closed arm. Being on the open arm seems to be an aversive experience, since rats have an innate fear of height and openness (Treit, Menard, & Royan, 1993). This would allow the animal to learn inhibitory avoidance if repeatedly placed inside the enclosed arm to explore the maze. On the other hand, when the rat is placed at the end of one of the open arms it can move towards the closed arm, presumably performing an escape response. The pharmacological exploration of the T-maze showed that these two defensive tasks are differently affected by drug treatments. Thus, compounds representative of three classes of anxiolytics - namely the agonist of BZD receptors diazepam, the serotonin 5-HT_{1A} agonist buspirone, and the nonselective 5-HT₂ antagonist ritanserin - have been shown to selectively impair inhibitory avoidance while leaving escape unchanged. These results are compatible with the view that inhibitory avoidance relates to GAD. In contrast, the escape task is insensitive to different classes of anxiolytics, and is impaired by chronic, but not acute administration of imipramine, clomipramine and fluoxetine, drugs that are used to treat PD.

Figure 1 (upper panel) shows the latency to leave the arms of the elevated T-maze on 3 consecutive trials. It can be seen that the latency to leave the enclosed arm increases across trials, indicating the acquisition of inhibitory avoidance. Latency to leave one of the T-maze open arms (escape) or one of the arms of a maze consisting of three enclosed arms (control) did not significantly change across trials. As shown in the lower panel of Figure 1, plasma levels of corticosterone are significantly higher in animals that acquired inhibitory avoidance, once again indicating the differential activation of the HPA axis on GAD and PA-associated behaviors.

Tests with human experimental anxiety

The main psychological procedures for inducing experimental anxiety in human beings for pharmacological studies have been the aversive conditioning of the skin conductance response and the simulated public speaking (SPS) tests. While the drug

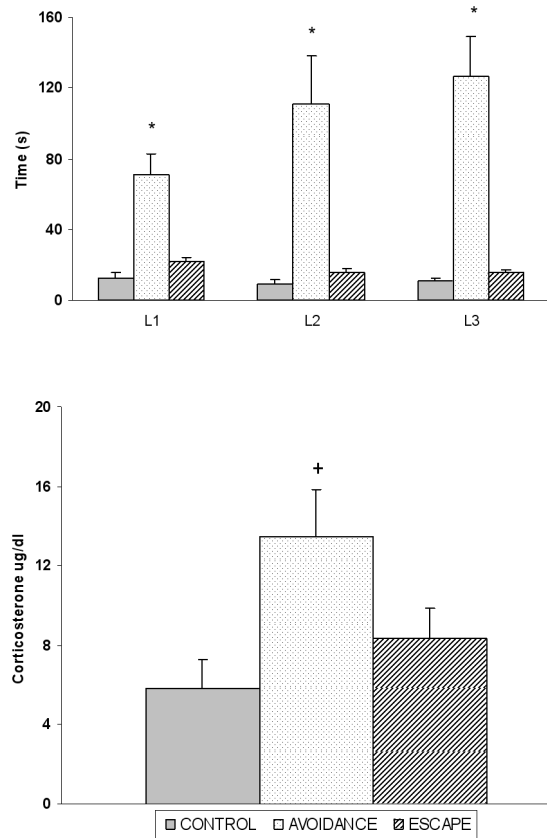


Figure 1. Upper panel: Bar chart comparing latencies (mean \pm SEM) taken by rats to withdraw from an enclosed arm of an elevated T-maze (control) or from the enclosed (avoidance) or open (escape) arm of the elevated T-maze, in three consecutive trials (L1, L2 and L3). * $P < .05$ (Duncan's test) compared with all other groups. Lower panel: Mean \pm SEM of plasma corticosterone levels measured immediately after the performance of control, avoidance and escape tasks. + $P < .05$ (Duncan's test) compared with the control group.

profile of the former is similar to that of GAD, SPS has a pharmacological profile that resembles PD and social anxiety disorder, and is believed to mobilize the same neural network that is involved in these disorders (for a review, see Graeff, Parente, Del-Ben, & Guimarães, 2003). As a consequence, two studies have been conducted by our research group to investigate whether SPS would affect HPA axis functioning.

In the SPS test, each participant is requested to prepare a speech and talk in front of a videocamera, the performance being recorded on videotape. Anxiety and other subjective states are evaluated by a psychometric instrument, the Visual Analog Mood Scale (VAMS). Also, bodily symptoms related to anxiety are assessed by the Bodily Symptom Scale (BSS). In the first endocrinological study (Garcia-Leal et al., 2005), the participants were divided into three groups: 18 symptomatic panic patients, 16 nonsymptomatic, drug-treated panic patients, and 17 healthy controls. Along the experimental session, the VAMS anxiety index and the total score of the BSS were higher in symptomatic patients than in controls, nonsymptomatic patients lying in between. In every group, the level of salivary cortisol was high at the beginning of the experimental session, and decreased after 70 minutes. This fall parallels the decrease in the VAMS anxiety factor and in BSS ratings, and appears to reflect habituation of the initial, anticipatory anxiety evoked by exposure to the new and potentially threatening laboratory environment. Accordingly, there has been a positive correlation between the initial level of cortisol and VAMS anxiety scores for the three groups, taken together. Preparation and performance of speech raised the VAMS anxiety index and BSS scores to the initial levels, but failed to increase salivary cortisol measured along 60 minutes, starting at the end of the speech (Figure 2). Therefore, SPS does not seem to activate the HPA axis, in contrast to anticipatory anxiety.

The second study was aimed at evaluating the effects of escitalopram, a very potent and selective 5-HT reuptake inhibitor, on SPS (Garcia-Leal, Del-Ben, Leal, Graeff, & Guimarães, 2009). Healthy male volunteers received, in a double-blind randomized design, placebo ($n = 12$), 10 ($n = 17$) or 20 ($n = 14$) mg of escitalopram, two hours before the test. Both doses of escitalopram did not affect the increase in VAMS anxiety scores determined by speech preparation or performance, but prolonged the rise induced by SPS. The most important results for the present argument are that the test itself did not significantly change cortisol plasma levels; neither did it change the levels of prolactin. Therefore, once more SPS failed to activate the HPA axis. However, under the highest dose of escitalopram, cortisol and prolactin increased immediately after the SPS (Figure 3). The last result suggests that 5-HT modulates the release of stress hormones.

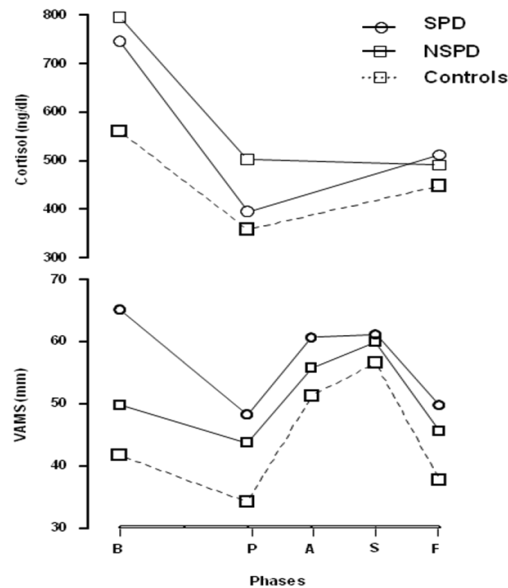


Figure 2. Upper panel: Mean salivary cortisol concentration before and after the simulated public speaking (SPS) test, measured in 18 symptomatic panic patients, 16 nonsymptomatic patients and 17 healthy controls. The initial measure was taken 25 minutes after the subject arrived in the laboratory. The last measure is the average of the highest value for each participant along 60 minutes starting at end of the speech. Measurements were taken immediately, 15, 30 and 60 minutes after the speech. Lower panel: Mean VAMS anxiety factor along the experimental session in the same subjects. Session phases are: B – initial, P – pre-test, A – speech preparation, S – speech performance, F – final.

In contrast to the above SPS test, a similar procedure known as the Trier Social Stress Test (TSST), in which the participant faces an audience and is requested to perform arithmetical calculations (Kirchbaum, Pirke, & Hellhammer, 1993), has been shown to increase salivary cortisol in normal volunteers, but fail to do so in PD patients (Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010). These results further support the view that PD patients lack cortisol responsivity to acute uncontrollable psychosocial stress. This unresponsiveness of the HPA axis seems to be rather specific, since in the mentioned study a normal cortisol awakening response in the morning has been recorded in the same patients.

Conclusions

The preceding evidence indicates that anxiety and panic are qualitatively different emotional states, which are related to the defense reactions to potential and proximal threat, respectively. Equally different are the related pathologies, GAD and PD, which differ both in their symptomatology and in the response to pharmacotherapy. Thus, specific neurobiological processes underlie each of these conditions. In regard

to stress hormones, the analyzed data suggest that while anxiety activates both the HPA and the sympatho-adrenal axes, the panic attack causes major sympathetic activation, but has little effect on the HPA axis.

At a more general level, the distinction between the hormonal responses to anxiety as compared to panic supports the view held by Palkovits that there are specific adaptive responses to each types of stress. This casts doubts on the existence of a GAS and, therefore on Selyes' original concept of stress itself. Even the alternative concept of stress as "a state of threatened to homeostasis" (Pacák & Palkovits, 2001) may be redundant to Cannon's notion of homeostasis, which implies that the organism tends to keep its internal state (Claude Bernard's *milieu intérieur*) within narrow limits through specific adaptive responses that tend to correct any provoked imbalance. Therefore, in spite of its major impact on research (heuristic value), on common knowledge and on every day life, the explanatory value of the concept of stress needs reevaluation.

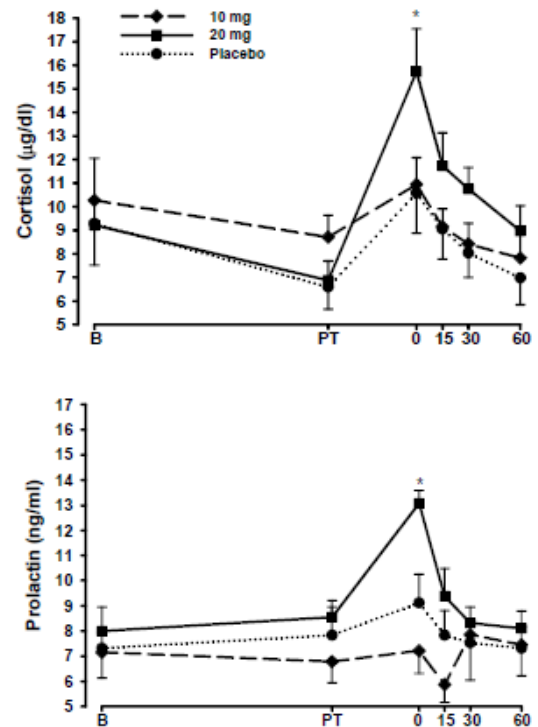


Figure 3. Plasma cortisol and prolactin levels along the SPS experimental session, measured in 37 healthy male volunteers treated with an acute oral doses of 10 mg ($n = 14$) or 20 mg ($n = 11$) of escitalopram, compared to placebo ($n = 12$). Measurements were taken 60 minutes after the arrival in the laboratory (B), two hours after drug or placebo intake and before the speech (P), as well as immediately (0), and 15, 30 and 60 minutes after the end of the speech. *Significantly different from PT and from other two groups.

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