

Anxiety, panic and the hypothalamic-pituitary-adrenal axis

Ansiedade, pânico e o eixo hipotálamo-pituitária-adrenal

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Abstract

Objective: This article focuses on the differential activation of the hypothalamic-pituitary-adrenal axis in generalized anxiety disorder and panic disorder. **Method:** The results of recently reported reviews of the literature are summarized and discussed. **Results:** 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 hypothalamic-pituitary-adrenal axis. Agonists of the cholecystokinin receptor B such as the cholecystokinin-4 peptide and pentagastrin increase stress hormones regardless of the occurrence of a panic attack and, thus, seem to activate the hypothalamic-pituitary-adrenal axis directly. The benzodiazepine antagonist flumazenil does not increase stress hormones, but this agent does not reliably induce panic attacks. Pharmacological agents that increase anxiety in both normal people and panic patients (caffeine, yohimbine, serotonergic agonists) raise stress hormone levels. **Conclusions:** In addition to the differences in symptomatology and pharmacological response, generalized anxiety disorder and panic disorder affect stress hormones in distinct ways. While anticipatory anxiety and generalized anxiety disorder activate both the hypothalamic-pituitary-adrenal and the sympathoadrenal axes, panic attack causes major sympathetic activation, but has little effect on the hypothalamic-pituitary-adrenal axis.

Descriptors: Stress; Hormones; Anxiety disorders; Hypothalamus; Pituitary-adrenal system

Resumo

Objetivo: Este artigo discute a ativação diferencial do eixo hipotálamo-pituitária-adrenal no transtorno de ansiedade generalizada e no transtorno de pânico. **Método:** Resultados de recentes revisões da literatura são resumidos e discutidos. **Resultados:** Os resultados de estudos experimentais que dosaram o hormônio adrenocorticotrópico, o cortisol e a prolactina mostram que ataques de pânico espontâneos, bem como os provocados por agentes panicogênicos seletivos – como lactato de sódio e dióxido de carbono –, não ativam o eixo hipotálamo-pituitária-adrenal. Agonistas do receptor de colecistocinina do tipo B, como o peptídeo colecistocinina-4 e pentagastrina, elevam os hormônios de estresse, independentemente da ocorrência de um ataque de pânico, parecendo ativar diretamente o eixo hipotálamo-pituitária-adrenal. O antagonista benzodiazepínico flumazenil não eleva o nível dos hormônios de estresse; porém, este agente farmacológico não induz ataques de pânico de modo consistente. Agentes farmacológicos que aumentam a ansiedade em pacientes de pânico (caféina, ioimbina, agonistas serotonérgicos), assim como em pessoas saudáveis, elevam o nível dos hormônios de estresse. **Conclusões:** Além das diferenças na sintomatologia e na resposta farmacológica, o transtorno de ansiedade generalizada e o transtorno de pânico afetam os hormônios de estresse de modo distinto. Enquanto a ansiedade antecipatória e o transtorno de ansiedade generalizada ativam tanto o eixo hipotálamo-pituitária-adrenal como o simpático-adrenal, o ataque de pânico causa acentuada ativação simpática; porém, afeta pouco o eixo hipotálamo-pituitária-adrenal.

Descritores: Estresse; Hormônios; Transtorno da ansiedade generalizada; Hipotálamo; Sistema hipófise-suprarrenal

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Introduction

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 Blanchard¹ has provided a sound criterion based on the systematic study of animal defensive strategies against predators. According to this view, 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. 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.

Gray and McNaughton have stressed an important difference between fear and anxiety that complements the above view.² For anxiety to occur, a drive to approach the danger stimulus is necessary, generating an approach-avoidance conflict. There is fear when the approach tendency is absent, and only the motivation to avoid or escape exists. This insight allows for the understanding of seemingly paradoxical psychopharmacological results: in contrast to responding suppressed by punishment (conflict tests) that is markedly released by anxiolytic agents like diazepam and other benzodiazepine receptor agonists, the performance of escape or avoidance tasks is either unaffected or even facilitated by the same class of drugs.³

Other experimental tasks sensitive to anxiolytics are conditioned freezing and conditioned suppression. In both cases, a formerly neutral stimulus becomes a predictor of harm through association with an unconditioned aversive stimulus (e.g., electric foot shock), according to the Pavlovian paradigm. As a consequence, the conditioned stimulus elicits freezing (conditioned emotional response – CER) and suppresses ongoing behavior (conditioned suppression). Anxiolytic agents attenuate these consequences.³ Thus, it may be said that the warning stimulus generates ‘anticipatory anxiety’, which, in my view, is a better name for this emotional state than the commonly used ‘conditioned fear’. Defensive threat, such as the behavioral display that cats show in face of a dog, is another defense reaction related to anxiety, since it is similarly attenuated by anxiolytic drugs.³

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. In contrast, visceral pain induces behavioral quiescence, which is necessary for recovery.

Defensive fight is an alternative adaptive reaction against proximal danger, which occurs when flight is impossible, but this strategy relates to rage, rather than panic. Nevertheless, the expression ‘fight/flight reaction’ is often used to describe the animal response to proximal threat.

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).⁴ In addition to the different clinical manifestations, the pharmacological profile of these disorders also varies: GAD is rapidly ameliorated by anxiolytic drugs, PD by chronic administration of

antidepressants, and phobias are resistant to known pharmacological treatment. The exception is social phobia, which responds to chronic antidepressants and, for this reason, has been renamed as social anxiety disorder (SAD).⁵

Emotions, either normal or abnormal, manifest themselves in different psychological (cognitive, affective, behavioral) and physiological (neurovegetative, neuroendocrine) domains. The central question to the present article is whether anxiety/GAD and panic/PD differ qualitatively or only quantitatively as to the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is the neuroendocrine hallmark of the stress response.

Stress

The concept of stress is based in the observation that different kinds of physical or psychological conditions that threaten the organism’s homeostasis elicit the same set of bodily changes, the so-called ‘general adaptation syndrome’.⁶ The most characteristic stress response is the release of the adrenocorticotrophic hormone (ACTH) and corticoids (cortisol in humans and cortisone in rats) into the blood stream as a result of activation of the HPA axis. The stimuli or situations that elicit the general adaptation syndrome are called stressors and the organism response is the stress reaction. 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’.⁷ 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.

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 the 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.⁸

The neural circuits that mediate 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 through 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 from the anterior pituitary in stressful conditions.⁹

Panic

To undergo a panic attack (PA) is one of the most overwhelming experiences that a person can endure, and certainly more stressful than generalized anxiety. Therefore, it is expected that the HPA axis would be activated to a greater extent by panic than by anxiety. Yet, the majority of the reported results indicate that the HPA axis is little affected by the PA.

In a recent review of the literature performed by Garcia-Leal et al., MEDLINE was searched looking for articles in which stress hormones had been measured during naturally occurring

PAs or during PAs experimentally induced by several panicogenic agents.¹⁰ The results have shown 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 cholecystokinin receptor B, such as cholecystokinin-4 peptide 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 PAs. Pharmacological agents that increase anxiety in both normal subjects and panic patients raised stress hormone levels. Among them are the α_2 -adrenergic antagonist yohimbine, the serotonergic agents 1-(m-chlorophenyl) piperazine (mCPP) and fenfluramine, as well as the psychostimulant caffeine. Therefore, the PA does not seem to activate the HPA axis, in contrast to anticipatory anxiety.

Naturally occurring PAs can be considered traumatic stressors.¹¹ Therefore, one would expect a marked ACTH and cortisol release following a PA. At the onset of the disorder, this might be the case, since the HPA axis responsivity to mild stress seems to be normal in children of parents with PD,¹² but in adult PD patients, responsiveness to both mild stress,¹³ as well as following a combined dexamethasone/corticotropin-releasing hormone test,¹⁴ has been reported to be reduced. As a result, it has been suggested that the HPA axis becomes progressively subsensitized in PD patients after repeated exposure to PAs.¹⁵ Another possibility is the uncoupling of the HPA axis and the noradrenergic system in PD.¹⁶ It is well known that the sympathoadrenal axis is markedly activated during the PA. According to this view, the PA would engage Cannon's emergency response independently of Selye's general adaptation syndrome.

A recent trial carried out in our laboratory with an experimental anxiety test of simulation of public speaking (SPS) supports this hypothesis. SPS is believed to mobilize the same neurobiological mechanisms that are involved in SAD and PD and, indeed, the pharmacological profile of SPS is similar to that of these disorders.¹⁷ In the mentioned study,¹⁸ the participants were divided into three groups: 18 symptomatic panic patients, 16 nonsymptomatic, drug-treated panic patients, and 17 healthy controls. Throughout the experimental session, subjective anxiety – measured by the Visual Analog Mood Scale (VAMS) and by the total score of the Bodily Symptom Scale (BSS) – was higher in symptomatic patients than in controls, nonsymptomatic patients lying in between. Measures of salivary cortisol taken at home have shown that the level was higher at 9 am than at 11 pm in every group, indicating a normal circadian regulation of the HPA axis in panic patients. Also, in every group the level of cortisol was high at the beginning of the experimental session and decreased after 70 min. This reduction parallels the decrease in the VAMS anxiety factor and in BSS ratings and appears to reflect habituation of the initial, anticipatory anxiety. Accordingly, there has been a positive correlation between the initial level of cortisol and VAMS anxiety for the three groups, taken together. Preparation and performance of speech raised the anxiety index and BSS scores to the initial levels, but failed to increase salivary cortisol measured during 60 min, starting at the end of the speech. Therefore, SPS does not seem to activate the HPA axis, as reported in panic attacks and in contrast anticipatory anxiety.

Anxiety

Both the HPA axis and the sympathoadrenal axis are activated by anticipatory anxiety.⁸ 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.¹⁹ In chronic anxiety, however, long-term activation of the HPA axis may become harmful, since corticoids hamper resilience mechanisms in the hippocampus, as discussed next.

According to Deakin and Graeff, an important mechanism to cope with chronic stress is the gradual development of a disconnection between the stressor and its behavioral consequences.⁴ This allows the person to function normally, despite the presence of annoying events that cannot be escaped or avoided. The hippocampus is thought to play a critical role in the development of resilience, the failure of this mechanism leading to depression.

Preclinical evidence has shown that 5-HT_{1A} receptors in the hippocampus facilitate the development of tolerance to chronic stress. Corticoids decrease the sensitivity of hippocampal 5-HT_{1A} receptors, impairing the coping mechanism. Accordingly, in the major depressive disorder, the feedback regulation of cortisol blood level is damaged, resulting in constant high levels of circulating cortisol. This would desensitize the hippocampal 5-HT_{1A} receptors, perpetuating the clinical condition. A key mechanism of action of antidepressant agents is to enhance the efficacy of 5-HT neurotransmission, which occurs following chronic treatment. In the hippocampus, this would restore the capacity to tolerate chronic stress (for reviews of this topic and original references, see references²⁰⁻²¹).

Conclusions

Anxiety and panic seem to be qualitatively different emotional states that are related to two types of defense reaction to potential and proximal threat, respectively. Equally distinct are the related pathologies, GAD and PD, which differ both in their symptomatology and in the response to pharmacotherapy, thus indicating that specific neurobiological systems are involved in each disorder. In particular, these conditions promote differential mobilization of stress hormones: while anxiety activates both the HPA and the sympathoadrenal axes, panic attack causes major sympathetic activation, but has little effect on the HPA axis.

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References

1. Blanchard DC, Blanchard RJ. Ethoexperimental approaches to the biology of emotion. *Annu Rev Psychol.* 1988;39(1):43-68.
2. Gray JA, McNaughton N. The neuropsychology of anxiety. 2nd edition. Oxford: Oxford University Press; 2000.
3. Graeff FG, Zangrossi Jr H. Animal models of anxiety disorders. In: D'haenen H, Den Boer JA, Westenberg H, Willner P, editors. *Textbook of biological psychiatry.* London: John Wiley & Sons; 2002. p. 879-93.
4. Deakin JFW, Graeff FG. 5-HT and mechanisms of defense. *J Psychopharmacol.* 1991;5:305-15.
5. Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectr.* 2005;10(1):49-56.
6. Selye H. A syndrome produced by diverse noxious agents. *Nature.* 1936;138(1):32.

7. Cannon WB. The emergency function of the adrenal medulla in pain and the major emotions. *Am J Physiol.* 1914;33(2):356-72.
8. Mason JW. A historical view of stress field. *J Hum Stress.* 1975;1:6-12.
9. Van de Kar LD, Blair ML. Forebrain pathways mediating stress-induced hormone secretion. *Front Neuroendocrinol.* 1999;20(1):1-48.
10. Graeff FG, Garcia-Leal C, Del-Ben CM, Guimaraes FS. Does the panic attack activate the hypothalamic-pituitary-adrenal axis? *An Acad Bras Cienc.* 2005;77(3):477-91.
11. McNally RJ, Lukach BM. Are panic attacks traumatic stressors? *Am J Psychiatry.* 1992;149(6):824-6.
12. Battaglia M, Bajo S, Strambi LF, Brambilla F, Castronovo C, Vanni G, Bellodi L. Physiological and behavioral responses to minor stressors in offspring of patients with panic disorder. *J Psychiatr Res.* 1997;31(3):365-76.
13. Stones A, Groome D, Perry D, Hucklebridge F, Evans P. The effect of stress on salivary cortisol in panic disorder patients. *J Affect Disord.* 1999;52(1-3):197-201.
14. Schreiber W, Lauer CJ, Krumrey K, Holsboer F, Krieg JC. Dysregulation of the hypothalamic pituitary-adrenocortical system in panic disorder. *Neuropsychopharmacology.* 1996;15(1):7-15.
15. van Duinen MA, Schruers KR, Maes M, Griez EJ. CO2 challenge induced HPA axis activation in panic. *Int J Neuropsychopharmacol.* 2006;1(1):1-8.
16. Coplan JD, Pine D, Papp L, Martinez J, Cooper T, Rosenblum LA, Gorman JM. Uncoupling of the noradrenergic-hypothalamic-pituitary-adrenal axis in panic disorder patients. *Neuropsychopharmacology.* 1995;13(1):65-73.
17. Graeff FG, Parente A, Del-Ben CM, Guimarães FS. Pharmacology of human experimental anxiety. *Braz J Med Biol Res.* 2003;36(4):421-32.
18. Garcia-Leal C, Parente AC, Del-Ben CM, Guimaraes FS, Moreira AC, Elias LL, Graeff FG. Anxiety and salivary cortisol in symptomatic and nonsymptomatic panic patients and healthy volunteers performing simulated public speaking. *Psychiatry Res.* 2005;133:(2-3)239-52.
19. Soravia LM, Heinrichs M, Aerni A, Maroni C, Schelling G, Ehlert U, Roozendaal B, de Quervain DJ. Glucocorticoids reduce phobic fear in humans. *Proc Natl Acad Sci U S A.* 2006;103(14):5585-90.
20. Graeff FG, Guimaraes FS, De Andrade TG, Deakin JF. Role of 5-HT in stress, anxiety and depression. *Pharmacol Biochem Behav.* 1996;54(1):129-41.
21. Guimaraes FS, Del Bel EA, Padovan CM, Netto SM, de Almeida RT. Hippocampal 5-HT receptors and consolidation of stressful memories. *Behav Brain Res.* 1993;58(1-2):133-9.