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A Hypothetical Explanation of Panic Disorder

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Abstract

Panic attacks may result from severe reduction of dehydroepiandrosterone (DHEA) in a person of low DHEA with normal or increased levels of cortisol. That is, an excessive ratio of cortisol to DHEA occurs which extinguishes the effects of unstable DHEA and magnifies the effects of cortisol. Prolactin increases during panic attacks and is correlated with attack severity. That is, prolactin increases to stimulate DHEA, but the response is inadequate to stabilize the DHEA to cortisol ratio and inhibit prolactin production. Therefore, prolactin remains elevated during an attack. Panic attacks occur when the effects of excessive cortisol excite prolactin stimulation of DHEA in a person who cannot respond with adequate DHEA (German J Psychiatry 2001;4:40-42).

Keywords: cortisol, cholecystokinin, dehydroepiandrosterone, panic disorder, prolactin

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Introduction

The physiological mechanism of panic attacks is unexplained. I suggest panic attacks occur because of an acute reduction in availability of the major adrenal steroid hormone, dehydroepiandrosterone (DHEA) in people who already produce low levels. My primary hypothesis is DHEA optimizes transcription and replication of DNA. Therefore, all tissues are activated by DHEA. It follows that DHEA activates the brain. Therefore, consciousness is a function of times of high DHEA and sleep is a time of low DHEA. I think cortisol, the second major adrenal steroid hormone, evolved to counteract the effects of DHEA during aggressive, potentially harmful or lethal, conflicts. Antagonism of DHEA by cortisol may be the basis of "fight or flight," which has high survival value. Cortisol production causes stress. The ratio of DHEA to cortisol should affect all tissues, especially neurological tissues, and becomes pathological in individuals who experience panic attacks.

Cortisol is involved in panic attacks. One study of panic attacks reported "subtle but significant elevation of cortisol levels" compared to controls, however, these levels did not correlate significantly with the severity of panic attacks (Bandelow, *et al*., 2000a). A subsequent study found nocturnal cortisol levels tend to be higher and "occurred mainly in more severely ill panic patients." (Bandelow, *et al*., 2000b). Another study confirms lack of high cortisol levels with all panic attacks, *i.e.*, plasma cortisol was elevated only during some attacks (Cameron, *et al*., 1987). Cortisol is connected to panic attacks, but cortisol levels, alone, do not cause panic attacks

Cholecystokinin (CCK) increases cortisol and provokes panic attacks, even in some healthy subjects. "In seven subjects, cholecystokinin-4 provoked a short-lasting (one to four minutes) panic-like attack (an intense unexplainable fear) at doses between 20 and 100 micrograms. In the other three subjects, doses of 80 to 100 micrograms induced severe anxiety, but no panic-like attack." (de Montigny, 1989). A larger study of healthy individuals of two different age groups (20-35 years- and 65-81 years-old) treated with CCK found "cortisol was significantly greater with CCK than with placebo," but the cortisol levels "were not correlated with symptom severity, suggesting that other factors may have contributed to the differential effect of panic on the HPA axis." (Flint, *et al*., 2000). In patients with panic disorder, CCK consistently stimulated panic attacks identical to spontaneous panic attacks (Bradwejn, *et al*., 1990).

Prolactin production increases during spontaneous panic attacks and panic attacks induced by CCK (de Montigny, 1989). In the study of CCK in healthy adults of differing

ages, Flint, *et al*., found that "maximum increase in prolactin, ACTH and cortisol was significantly greater with CCK," compared to placebo (Flint, *et al*., 2000). More importantly, prolactin correlates with the severity of spontaneous panic attacks. "Plasma prolactin was elevated at the peak of most of the attacks and correlated with attack severity." (Cameron, *et al*., 1987). Prolactin levels are directly tied to panic attacks and their severity.

I suggest the increase in prolactin during spontaneous panic attacks and during "panic-like attacks in healthy volunteers" induced by CCK (de Montigny, 1989) represent a mechanism for increasing DHEA during attacks. In young baboons, prolactin specifically stimulates DHEA: "in contrast to ACTH, the action of PRL [prolactin] on the adrenal is apparently specific for androgen [DHEA] production." (Pepe, 1985). Hyperprolactinemia occurs with elevated DHEAS in women. When hyperprolactinemia is reduced with bromocriptine, DHEAS levels are reduced without changes in cortisol levels (Schiebinger, et al., 1986). Reducing prolactin reduces DHEAS. (DHEA sulfate, DHEAS, is the large supply of DHEA available in blood. The active molecule, DHEA, is derived from this supply.)

Fava, *et al*., measured the ratio of DHEAS to cortisol in panic disorder. They examined this ratio because the ratio had "been used as an index of adrenocortical function, [they hypothesized the ratio] would be altered in panic disorder patients and would change after treatment." They reported "No significant differences were noted between pretreatment and posttreatment DHEA-S/cortisol ratio values in patients treated with alprazolam(n = 8), in patients treated with clonazepam (n = 13), or in patients treated with placebo (n = 3)." Of importance to this treatise is their finding that "The DHEA-S/cortisol ratio values in the 24 patients with panic disorder (mean = 20.5, SD = 11.6) were significantly higher than those of a group of 60 normal controls (mean = 11.5, SD = 6.01) and were also significantly higher than those of a group of 22 depressed patients (mean = 10.6, SD = 6.33)." (Fava, *et al*., 1989)

If one assumes that DHEA is the active molecule, the findings of Fava, *et al*., may be explained. Patients with panic disorder may produce significantly less DHEA than controls and depressed patients because panic attack patients are not producing DHEA from DHEAS, so their DHEAS to cortisol ratio is very high. Fava, *et al*., also found no differences when their patients were treated with alprazolam. However, Kroboth, *et al*., report that alprazolam increases DHEA significantly in "healthy volunteers (25 young men, aged 22-35, and 13 elderly men, aged 65-75)." "Alprazolam produced (1) significant increases in DHEA concentrations at 7 hours in both young and elderly men; (2) significant decreases in cortisol concentrations; and (3) no change in DHEA-S concentrations." (Kroboth, *et al*., 1999). The lack of change in DHEAS levels may suggest the conversion from cortisol to DHEA in healthy individuals.

DHEA reduces prolactin levels (Milewich, *et al*., 1995). A sufficiently high level of DHEA inhibits prolactin production. This is a cyclic mechanism involving prolactin and DHEA. Healthy individuals produce sufficient DHEA to reduce prolactin levels. Patients with panic attack disorder who produce very low DHEA cannot reduce prolactin by feedback inhibition from DHEA. This is why "Plasma prolactin was elevated at the peak of most of the attacks and correlated with attack severity." (Cameron, *et al*., 1987).

It is my hypothesis that DHEA stimulates consciousness during the day and declines at night, to allow sleep. During sleep, I think DHEA declines to lowest levels during delta (slow-wave) sleep, with levels maintained just sufficient to support cardiovascular activity. This level is maintained by the cyclic mechanism involving prolactin. When DHEA declines to low levels, prolactin increases and stimulates sufficient DHEA to maintain the brainstem. When this cycling occurs, DHEA levels overshoot and decrease prolactin. This extra DHEA stimulates the brain. This slight increase in DHEA during sleep activates the brain and produces REM sleep or dreaming. Therefore, according to my model of sleep, delta sleep represents a time of low DHEA and REM sleep represents a time of higher DHEA during sleep. Kronenberg, *et al*., administered CCK to healthy subjects during REM sleep and delta sleep. CCK produced panic attack-like effects of greater intensity during the time of lowest DHEA, that is, delta sleep. "In nine subjects, stimulation with 50 µg CCK-4 during REM sleep failed to elicit a full-blown panic awakening, while the same dose, administered during delta sleep, produced full-blown panic attacks in two participants. Similarly, stimulation of six subjects with 100 µg CCK-4 during REM sleep resulted in only one panic response, whereas four of nine subjects awoke experiencing a panic attack following stimulation with the identical dose during delta sleep. Severity of panic symptomatology, as measured by the self-rated Acute Panic Inventory, was also significantly increased when CCK-4 was administered during delta sleep." (Kronenberg, *et al*., 2001). This study supports a connection of low DHEA with panic attacks. Since Bandelow, *et al*., 2000b, found higher levels of nocturnal cortisol in "more severely ill panic patients" and Abelson and Curtis also reported "overnight hypercortisolemia" in panic disorder (Abelson and Curtis, 1996), this could indicate conversion from DHEA to cortisol in panic disorder.

Panic attacks may be due to very low DHEA levels relative to cortisol levels, possibly resulting from conversion of DHEA to cortisol. Therefore, normal levels of cortisol may predispose an individual to panic attacks even without a triggering event. If cortisol levels are high relative to DHEA between attacks, the individual may experience intermittent or continuous anxiety. Therefore, any latent physiological or psychological change which increases the cortisol to DHEA ratio could excite a panic attack. Prolactin levels increase during panic attacks and are directly connected to severity.

Prolactin increases to stimulate DHEA. Since prolactin levels are decreased by DHEA and panic attack sufferers cannot produce sufficient DHEA, prolactin levels remain high and connected with the panic attack. Panic attacks result from the inability to respond to excess cortisol relative to DHEA.

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