



A panic attack-like unusual stress reaction

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ABSTRACT

Ever since the seminal studies of Hans Selye, activation of hypothalamus-pituitary-adrenal (HPA) axis is emblematic of stress. Consequently, the lack of HPA axis responses following the undisputable psychological stress of a panic attack stands out as one of the most intriguing findings of contemporary psychiatry. On the other hand, the defensive behaviors and aversive emotions produced by stimulation of the dorsal periaqueductal gray matter (DPAG) have been proposed as a model of panic attacks. Therefore, we examined whether the plasma levels of 'stress hormones' corticotropin and prolactin show any change following the DPAG-evoked freezing and flight behaviors of the rat. Rats bearing an electrode into the DPAG and an intra-atrial catheter were stimulated at 9:00 a.m., 18–24 h after the catheter implantation. Blood samples were withdrawn just before 1-min stimulation of DPAG, immediately after (5 or 15 min) and throughout 3 to 27 h following stimulation. In another experiment, samples were withdrawn either before or following a prolonged stimulation (5 min) of the DPAG with flight threshold intensity. Hormones were measured by either chemiluminescent or double-antibody immunoassays. Hormone plasma levels following freezing and flight behaviors were compared to those of resting or restraint-stressed rats. Data show that stress hormones remain unaltered following the DPAG-evoked defensive behaviors. Not even the 5-min stimulation of DPAG with the flight threshold intensity changed corticotropin plasma levels significantly. As far as we know, this is the first demonstration of the lack of stress hormone responses following the intense emotional arousal and physical exertion of a fear-like behavior in rats. Data add new evidence of DPAG involvement in spontaneous panic attacks.

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Introduction

Hans Selye (1936, 1976) theory of stress had a major impact on medical world and the full implications of his assertions were threshed out over almost a century. Particularly, clinical and experimental studies carried out in the last decades implicate the stress response in the development of major depression, panic and posttraumatic stress disorders (Strohle and Holsboer, 2003). Selye's hallmark was but the concept of the non-specificity of hypothalamus-pituitary-adrenal (HPA) axis activation following the exposure of the organism to an astonishing variety of stressors both physical and psychological (Selye, 1936, 1976). Eventually, it was shown that prolactin (PRL) was likewise released in most stressful conditions (Siegel et al., 1980). Accordingly, evidence showing the lack of corticotropin (ACTH), cortisol (CORT) and PRL responses following the undeniable stress of a panic attack are among the most puzzling findings of contemporary psychiatry (Liebowitz et al., 1985a; Levin et al., 1987; Woods et al., 1987, 1988;

Hollander et al., 1989a,b; Kellner et al., 1998). The HPA axis unresponsiveness during panic attacks is in contrast with its basal hyperactivity in panic patients. Indeed, panic patients show an enhanced ACTH response to the administration of corticotropin releasing hormone (CRH) following the HPA axis peripheral suppression with dexamethasone (Schreiber et al., 1996; Erhardt et al., 2006).

Nevertheless, the HPA axis unresponsiveness in panic attacks has been debated up to the present days (Hollander et al., 1989c; Graeff et al., 2005). As a matter of fact, panic patients very often present anticipatory anxiety and comorbid disorders that might be responsible for the eventual activation of HPA axis in clinical studies (Lopez et al., 1990). On the other hand, the HPA axis is activated by anxiety-inducing drugs (beta-carboline, yohimbine, metrazol and fenfluramine) and putative panicogens of which the cholecystokinin (CCK)-related peptides were best studied. Also, because spontaneous panic attacks are unpredictable, the lack of neuroendocrine responses was most often observed in lactate- and carbon dioxide (CO₂)-induced panic attacks. Therefore, in spite of the marked similarities of these panic attacks with the clinical ones (Klein, 1993), it has been argued whether the negative results could also be extended to spontaneous panic attacks. As a matter of fact, in one of the few studies on spontaneous

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panic attacks, Cameron et al. (1987) did not observe any significant increase in CORT and PRL plasma levels either at the peak or 10 and 60 min after 9 spontaneous panic attacks in 4 panic disorder patients. Likewise, neither of these hormones changed following the situational panic attacks of 15 drug-free agoraphobic patients (Woods et al., 1987). Actually, PRL responses tended to be smaller in patients as compared to controls. Accordingly, the latter authors suggested that the chronically recurrent panic attacks might have caused an adaptation of neuroendocrine mechanisms. Nevertheless, Aneegg et al. (2002) showed that whereas the PRL plasma levels did not change, there was a decrease in CORT saliva levels following the dive-induced panic attacks of scuba divers during an emergency training in a natural setting. While these authors attributed the decrease in saliva CORT to a mouth rinsing during the dive, PRL plasma levels of panic-resistant divers during the emergency trial were markedly higher than those of panicking ones. This study is particularly important given the close relationship of diving emergency with the risk of suffocation (Klein, 1993).

On the other hand, the stimulation of the dorsal half of periaqueductal gray matter (DPAG) produces aversive emotions and visceral responses in humans (Nashold et al., 1969; Young, 1989) and unconditioned defensive behaviors in rats (Bittencourt et al., 2004, 2005) that have been proposed as a model of panic attacks (Gentil, 1988a; Deakin and Graeff, 1991; Jenck et al., 1995; Schenberg et al., 2001). Indeed, whereas the stimulation of DPAG with stimuli of lower magnitude produces a freezing response reminiscent of a crisis of agoraphobia, higher stimuli give rise to a vigorous flight behavior made up of gallops and jumps of about 1 m/s and 50 cm height, respectively. These behaviors are accompanied by cardiovascular and respiratory responses and, less often, micturition and defecation (Carobrez et al., 1983; Schenberg et al., 1983, 1993, 2005; Bittencourt et al., 2004). Moreover, because rats learn to switch-off the stimulus, stimulation of DPAG is likely to produce an aversive motivational state (Olds and Olds, 1963; Schenberg and Graeff, 1978).

Most importantly, DPAG-evoked galloping of the rat 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 administrations of the serotonin selective reuptake inhibitors clomipramine (5–10 mg/kg/day) and fluoxetine (FLX, 1 mg/kg/day), respectively. In contrast, freezing response was selectively attenuated by maprotiline (10 mg/kg/day), a noradrenaline selective reuptake inhibitor that lacks a conspicuous antipanic activity. In addition, neither the acute administration of antidepressants and diazepam (Schenberg et al., 2001; Vargas and Schenberg, 2001), nor the acute and 10-day administration of buspirone (unpublished results), attenuated the DPAG-evoked behaviors. Conversely, DPAG-evoked galloping was selectively facilitated by peripheral injections of pentylenetetrazole (Schenberg et al., 2001), a putative panicogen in humans (Gentil, 1988b). In the same vein, whereas the DPAG-evoked escape in the shuttle-box paradigm was facilitated by systemic injections of panic-inducing drugs yohimbine and caffeine, this response was attenuated by both the CCK-2 receptor antagonists and the high-potency panicolytic benzodiazepines alprazolam and clonazepam (Jenck et al., 1995, 1996).

The above pharmacological data suggest that galloping is the panic attack best model (Schenberg et al., 2001). Be this as it may, neither the HPA axis activation, nor the PRL response would be expected following the flight behavior produced by electrical stimulation of DPAG. Therefore, we examined whether there is any change in both ACTH and PRL plasma levels following the DPAG-evoked freezing and flight behaviors of the Wistar albino rat.

Methods

Animals

Wistar male albino rats weighing 230–250 g ($n=70$) were housed in individual cages kept in a temperature- (23–25 °C) and light-controlled room (12×12 h light/dark cycle, lights on at 7:00 a.m.). Experiments conformed to the National Institutes of Health

(NIH) and Brazilian Neuroscience and Behavior Society (SBNeC) guidelines on the ethical use of animals.

Surgery

Rats anesthetized with 400 mg/kg (i.p.) chloral hydrate (Isofar, Rio de Janeiro, Brazil) were fixed on a stereotaxic instrument (David Kopf, Tujunga, USA) with the skull horizontal between bregma and lambda. Anaesthesia was complemented by the infiltration of the scalp with 1% lidocaine plus 0.005% epinephrine (Cristália, São Paulo, Brazil). Following the incision, the subcutaneous tissues were cut out and the bone over the lambda was abraded with a diamond-coated dentistry drill (KG Sorensen, São Paulo, Brazil), thereby allowing the bone removal and sinus exposure. Monopolar electrodes were made of a stainless steel wire (0.25 mm o.d.) (California Fine Wire Company, Grover City, USA) insulated throughout except at the cross section of the tip. Electrode implantation was facilitated by a small incision in the dura just by the sinus. Whenever necessary the sinus was gently pushed, allowing the electrode penetration to the aimed site. The pieces were joined altogether with autopolymerizing dentistry resin and anchored to the skull by means of 4 stainless steel screws. At the end of surgery, the rats received 24,000 IU of penicillin-G benzathine (i.m.) and were placed over a heated platform until their full recovery.

Brain stimulation

Stimulation screening sessions were carried out in a sound-attenuated temperature-controlled room (23–25 °C). Following a surgery recovery of 5 to 7 days, rats were connected to a light cable and placed into a cylindrical plexiglass open-field of 50 cm wall height and diameter, in which they remained undisturbed for 30 min to get used to the environment and reduce spontaneous activity. Stimuli were then delivered by means of a custom-built constant current sine-wave stimulator and monitored through an oscilloscope (V-121, Hitachi-Denshi, Malaysia). A mercury swivel allowed the free movement of the rat throughout the stimulation session. Screening session stimuli consisted of 30 s sine-wave trains (0–70 μ A, 60 Hz, ac) spaced 30 s apart. The current was increased in 5 μ A steps (1.7 μ A, rms.) until the rat presented the first defensive response (exophthalmus or immobility). After that, stimuli were presented at 4 min intervals up to the elicitation of the flight behavior. Otherwise, session was halted at the cut-off intensity of 70 μ A (24.5 μ A, rms). Besides the eventual presentation of micturition and defecation, the individual components of DPAG-evoked defensive behaviors were recorded as follows:

Exophthalmus — Eyeball protrusion and fully opened eyelid.

Immobility — Overall behavioral arrest accompanied by tachypnoea and increased muscle tonus as suggested by the extension of neck and/or limbs and raising of head, trunk and/or tail.

Trotting — Fast locomotion with elevation of trunk and tail and alternating stance and swing movements of contralateral limbs.

Galloping — Running alternating stance and swing movements of anterior and posterior limb pairs.

Jumping — Upward leaps directed to the border of the open-field.

Threshold intensities of freezing (tense immobility plus exophthalmus) and flight (galloping, trotting or jumping) were selected for blood-sampling sessions.

Catheter implantation

Rats which stimulation in screening sessions produced gallops with peak-to-peak intensities below 70 μ A were anesthetized with chloral hydrate and implanted with an intra-atrial silastic catheter (1-mm diameter) inserted through the right jugular vein (the femoral vein cannulation was avoided to spare the hind legs for the flight effort).

Blood sampling

Brain stimulation and restraint-stress were always carried out at 9:00 a.m., 18 to 24 h after the catheter implantation. Handling stress was greatly minimized by remote blood withdrawal through a 40-cm polyethylene cannula (PE-10) adapted to the stimulation cable. Blood-sampling schedules were as follows:

Experiment-1: ACTH and PRL responses following passive (freezing) or active (flight) defensive behaviors

The day after the catheter implantation, the rat was placed in the open-field and stimulated with 1-min sine-wave pulse at freezing or flight threshold intensities, or with a subliminal stimulus, i.e., the maximum intensity that did not produce any defensive behavior in the screening session. Rats were assayed *a posteriori* according to the response exhibited in freezing (ACTH, $n=7$; PRL, $n=8$), flight (ACTH, $n=7$; PRL, $n=5$) and subliminal (ACTH, $n=5$; PRL, $n=11$) groups. ACTH and PRL plasma levels were assayed in separate groups from blood samples (0.5 ml) withdrawn just before (baseline) or 15 min, 1, 3, 6, 9 and 27 h following the onset of intracranial stimulus.

Experiment-2: Short-term ACTH responses following 1-min stimulation of DPAG with the flight threshold intensity

Rats were stimulated with 1-min sine-wave pulse trains at the flight threshold intensity. Blood samples were withdrawn immediately before (baseline) the stimulus onset, just after the stimulus terminus (5 min), or 15 min, 1 and 3 h after that. The ACTH plasma levels of DPAG-stimulated rats ($n=8$) were compared to sham-stimulated ($n=6$)

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