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Modeling panic attacks

Luiz Carlos Schenberg*, Athelson Stefanon Bittencourt, Eliana Cristina Murari Sudré, Leila César Vargas

Department of Physiological Sciences, Universidade Federal do Espírito Santo, Vitória, ES, Brazil

Abstract

The isomorphism of dorsal periaqueductal gray-evoked defensive behaviors and panic attacks was appraised in the present study. Thresholds of electrically induced immobility, trotting, galloping, jumping, exophthalmus, micturition and defecation were recorded before and after acute injections of anxiolytic, anxiogenic and antidepressant drugs. Antidepressant effects were further assessed 24 h after injections of 7–14- and 21-day treatments. Chronic administration of clomipramine (CLM, 5–10 mg/kg) a clinically effective antipanic drug increased the thresholds of immobility (24%), trotting (138%) galloping (75%), jumping (45%) and micturition (85%). The 21-day treatment with fluoxetine (FLX, 1 mg/kg) virtually abolished galloping without changing the remaining responses. Galloping thresholds were also increased by 5 mg/kg acute injections of CLM (19%) and FLX (25%). In contrast, chronically administered maprotiline (10 mg/kg), a noradrenaline (NE) selective reuptake inhibitor, selectively increased the thresholds of immobility (118%). Diazepam (1.8 mg/kg) and midazolam (MDZ, 2.5 mg/kg) failed in attenuating the somatic defensive responses. Yet, the sedative dose of MDZ (5 mg/kg) attenuated immobility. The panicogenic drug, pentylenetetrazole (50 mg/kg), markedly decreased the thresholds of galloping (−51%) and micturition (−66%). These results suggest that whereas immobility is a NE-mediated attentional response, galloping is the panic-like behavior best candidate.

Keywords: Panic; Fear; Anxiety; Periaqueductal gray; Locus coeruleus; Freezing; Flight; Clomipramine; Fluoxetine; Maprotiline; Diazepam; Midazolam; Pentylenetetrazole

1. The spontaneous panic attack

Spontaneous panic attacks are the core phenomenon of panic disorder. Typically, they are a sudden experience of intense distress, catastrophic threat and severe anxiety accompanied by marked autonomic and neurological symptoms including dyspnoea, hypertension, palpitation, chest pain, sweating, tremors and dizziness. Fleeing from the immediate situation, freezing (a 'block while walking'), choking and smothering sensations, or a feeling of difficulty in deep breathing, are quite frequent as well. Moreover, some patients fear losing control over anal or bladder sphincters [22,40].

Panic attacks can be provoked in patients by many chemicals, particularly by infusion of sodium lactate [62,63]. Comparison of spontaneous and lactate-induced panic attacks showed that most symptoms are similar, namely, fright in general, desire of fleeing, dyspnoea, chest pain and feeling hot/cold or both [40].

There are remarkable similarities, however, between panic attacks and the aversive responses evoked by stimulation of the dorsal half of the periaqueductal gray matter (DPAG). In humans, electrical stimulation of DPAG (0–5 mm lateral to aqueduct) produces intense anxiety, panic, terror and feelings of imminent death accompanied by diffuse medial pain in the face and 'around the heart' or 'deep in the chest', pulse increase (not correlated to chest pain), dyspnoea (apnoea, sighing or deep breathing), wide-open eyes, feelings of burn/cold, bladder sensations, voiding urges, and vibration sensation of the head, face or chest [65]. These responses are evoked from dorsal but not ventral half of the periaqueductal gray matter (PAG) [88]. It should be noted, however, that fear and anxiety were also reported following electrical stimulation of the medial hypothalamus, amygdala and hippocampus [25,47]. The amygdala and the tectum of the midbrain (DPAG and deep collicular layers) were but the only structures to light up during positron emission tomography of lactate-induced panic attacks [70]. Moreover, in contrast to the amygdala and hypothalamus, 'rage' does not ensue following electrical stimulation of DPAG in humans. Stimulation of the amygdala also

* Corresponding author. Address: Departmento de Ciências Fisiológicas, Centro Biomédico, Universidade Federal do Espírito Santo, Av. Marechal Campos 1468 (Maruípe) 29040-090 Victória-ES, Brazil. Tel.: +55-27-3335-7332; fax: +55-27-3335-7330.

E-mail address: schenber@terra.com.br (L.C. Schenberg).

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Table 1
Isomorphism of panic attacks in humans and stimulation of dorsal periaqueductal grey matter of both humans and rats. Abbreviations: n.a. data not available; n.o. response not observed; PET, position emission tomography (see text for references)

	Spontaneous or lactate-induced panic attacks in humans	Stimulation of dorsal periaqueductal grey matter in humans	Stimulation of dorsal periaqueductal grey matter in rats
Feelings/behavior	'Block while walking'	n.a.	Freezing behavior
	Desire of fleeing	Stimulus switch-off	Flight behavior
	Intense distress	Intense distress	Aversion
	Severe anxiety	Severe anxiety	–
	Panic, terror	Panic, terror	–
	Feeling of imminent death	'Scared to death'	–
	Fear of going crazy	n.a.	–
	Fear of losing control	n.a.	–
Autonomic responses	Tachypnoea	n.a.	Tachypnoea
	Hyperventilation	Hyperventilation	Hyperventilation
	Dyspnoea	Apnoea	n.o.
	Difficulty in deep breathing	Sighs, deep breaths	Deep breaths
	Tachycardia	Tachycardia	Tachycardia
	Hypertension	n.a.	Hypertension
	Bladder voiding urge	Bladder voiding urge	Micturition
	Peristalsis	n.a.	Defecation
	n.a.	Wide-open eyes	Exophthalmus
	Sweating	n.a.	n.a.
	n.a.	Piloerection	n.o.
Endocrine responses	No prolactin response	n.a.	No prolactin response
	No ACTH response	n.a.	No ACTH response
	No cortisol response	n.a.	n.a.
Neurological responses/ paresthesias	Sensation of tremor	Sensation of vibration	–
	Chest pain	Chest and heart pain	–
	Feeling hot/cold	'Burn/cold' sensations	–
	Dizziness	n.a.	–
	n.a.	Numbness	–
	n.a.	Face pain	–
Brain areas stimulated or activated in PET	Dorsal periaqueductal gray, deep layers of superior colliculus, amygdala (PET)	Dorsal periaqueductal gray and adjacent tectum (0–5 mm lateral to aqueduct) (X-rays)	Dorsal periaqueductal gray, deep layers of superior colliculus

differs in evoking a broad spectrum of emotions, including intense pleasure, associated with vivid imagery and the recollection of past emotional experiences [34].

Stimulation of DPAG has putative aversive properties for rats readily learn to switch-off the stimulus [72]. DPAG stimulation also produces unconditioned behaviors that are reminiscent of clinical and experimental panic attacks in humans. Therefore, rats may either freeze or show a full-blown flight behavior made up of galloping and jumping responses [76,77,82,85,86]. DPAG-evoked flight is accompanied by hypertension, tachycardia and tachypnoea. Yet, in contrast to human panic attacks, DPAG-evoked freezing behavior lacks the tachycardic response [74].

Notably, situational or lactate-induced panic attacks in humans [59,63] and DPAG-evoked freezing and flight behaviors in rats [75] are not accompanied by increases in the plasma levels of cortisol (humans), ACTH and prolactin (humans and rats) showing that these behaviors are not due to a generalized stress reaction.

Consequently, even though the DPAG-evoked responses of the rat have been formerly considered as a model of anxiety in operant procedures [43,72], DPAG-evoked innate responses have been recently proposed as a paradigm of human panic attacks [31,36,37,51,75]. The isomorphism of panic attacks and DPAG-evoked defensive behaviors is thus the main concern of the present study (Table 1).

2. Brain domains of fear and panic

Hess coined the term 'affective defense reaction' (affektiven Abwehrreaktion) to describe the behaviors produced by hypothalamic stimulation in cats, particularly, the immobile aggressive display with slightly hunched back, flattening of the ears, teeth baring, hissing, growling, unsheeted claws, piloerection and marked mydriasis [48]. This peculiar pattern of responses was preceded by arousal and progressive restlessness and could culminate in either