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Review

Sex determinants of experimental panic attacks

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ABSTRACT

Panic disorder is twice a common in women than in men. In women, susceptibility to panic increases during the late luteal (premenstrual) phase of the menstrual cycle, when progesterone secretion is in rapid decline. This article considers the evidence for the midbrain periaqueductal grey (PAG) as a locus for panic and for the use of PAG stimulation as an animal model of panic in both sexes. We show in females how a rapid fall in progesterone secretion, such as occurs during the late dioestrus phase of the ovarian cycle in rats (similar to the late luteal phase in women), triggers a neuronal withdrawal response during which the excitability of the midbrain panic circuitry increases as a result of upregulation of extrasynaptic $GABA_A$ receptors on inhibitory interneurones in the PAG. The withdrawal effect is due not to the native hormone but to its neuroactive metabolite allopregnanolone. Differences in the kinetics of allopregnanolone metabolism may contribute to individual differences in susceptibility to panic in women.

Contents

A panic attack is a form of sudden onset episodic anxiety, usually accompanied by marked autonomic changes. Attacks are characterised by sudden surges of intense fear or terror, a desire to flee, feeling of imminent death, going crazy or loosing control. Associated autonomic changes include palpitations, raised blood pressure, difficulty in deep breathing, sweating, urge to void the bladder and increased gut peristalsis (DSMIV). Those who experience repeated attacks are diagnosed as suffering from panic disorder (DSMIV); sufferers may develop anticipatory anxiety about the next attack and avoid places where a panic attack would be embarrassing. Ultimately, generalised avoidance or agoraphobia may ensue. At least two panic subtypes are thought to co-exist, one characterised by a respiratory component and a second class typified by general somatic symptoms (Roberson-Nay and Kendler, 2011). Panic attacks may occur mainly at night (nocturnal panic) and panic may present with agoraphobia. So far, differences in aetiology have not been shown.

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1. Panic in women

1.1. Incidence of panic in women

Panic attacks are surprisingly common. It has been estimated that 7–10% of the population will experience at least one panic attack during their lifetime and about 2–5% of the population have panic disorder (i.e., frequent and/or disabling panic attacks) (Goodwin et al., 2005). The lifetime prevalence of panic disorder in women is more than twice that of men (Eaton et al., 1994; McLean et al., 2011; Sheikh et al., 2002). Age is another confounding factor in women, in whom panic disorder is rare before puberty or after menopause. The peak age for onset occurs during the period of young adult hood (i.e. >15 years) and the incidence declines markedly in middle age (Eaton, 1995; Von Korff et al., 1985). Panic is therefore most common in premenopausal females.

1.2. Menstrual cycle and panic

Women with panic disorder commonly show menstrual cycle-linked fluctuations in the symptoms of panic anxiety. An increase in anxiety symptoms and in the frequency of panic attacks has been reported to occur during the late luteal (premenstrual) phase (Breier et al., 1986; Cameron et al., 1988; Kaspi et al., 1994; Sigmon et al., 2000 but see Stein et al., 1989). In susceptible individuals panic symptoms can also be induced experimentally by chemical provocation, e.g., by intravenous infusion of sodium lactate, CCK-4 or pentagastrin or by inhalation of CO_2-enriched air (Eser et al., 2007; Facchinetti et al., 1992; Lapierre et al., 1984; Liebowitz et al., 1986; Leibold et al., 2013). As with 'spontaneous' panic, responsiveness to such panicogenic challenges is enhanced during the premenstrual period (Landén and Eriksson, 2003; Nillni et al., 2011).

The premenstrual period is a time when many women who are not panic sufferers, as well as those who are, experience a constellation of adverse psychological symptoms known as premenstrual syndrome (PMS). These symptoms, which include irritability, mood swings and anxiety, are triggered by everyday stressful psychological challenges that, at other times of the monthly cycle, are not perceived as especially troublesome. PMS afflicts 30–80% of premenopausal women during the late luteal phase of their menstrual cycle, with a minority (around 5%) who experience extremely severe symptoms being classified as suffering from the psychiatric condition premenstrual dysphoric disorder (PMDD) (O'Brien et al., 2011).

Interestingly, patients with PMDD but no history of panic, showed a greater responsiveness to experimental panicogenic challenge than healthy control subjects (Le Mellédo et al., 1999, 2000; Gorman et al., 2001; Sandberg et al., 1993). Indeed panic can be induced both in PMDD sufferers and in patients suffering with panic disorder by administration of the benzodiazepine antagonist flumazenil, suggesting a common involvement of GABA systems in the two disorders (Le Mellédo et al., 2000; Nutt et al., 1990). The association between increased susceptibility to panic and development of PMS-like symptoms, together with the co-morbidity of panic and PMDD and the overlapping pharmacology, lend credence to the suggestion that PMDD may be a variant of panic disorder (Vickers and McNally, 2004). Equally, the reverse may hold true.

In terms of PMS, there is a clear link between onset of symptoms and cyclical changes in ovarian hormones; symptoms do not appear in anovulatory cycles (Bäckström et al., 2003; Hoyer et al., 2013). Ovulation itself is not the key factor however, since many women taking the combined contraceptive pill on a 21 day on, 7 day off dosing regimen, which prevents ovulation, also experience PMS-like symptoms that peak during the 7 day drug-free period (Coffee et al., 2008; Kadian and O'Brien, 2012). Comparable data are not available for panic sufferers who take the contraceptive pill. However, given the link between PMDD and susceptibility to panic during the late luteal phase in spontaneously cycling women (see above), withdrawal from progesterone may be a contributory factor that increases the susceptibility of women to panic as well as to developing PMS. In terms of PMS, symptoms occur at a time when blood levels of progesterone or synthetic progestins are dropping rapidly, i.e., during the late luteal phase or as women taking the contraceptive pill begin the 7 day drug-free period. Thus progesterone withdrawal may be the trigger for PMS. In this article we will explore possibility that withdrawal from progesterone also confers an increased susceptibility to panic in females.

2. Panic in animals

2.1. Animal models of panic

Progress in understanding the neuronal dysfunction that underlies the development of anxiety states such as panic is critically dependent on the availability of good animal models of the human condition (for critical analysis of animal modelling of human anxiety states see Donner and Lowry, 2013). Various animal models have now been developed in order to investigate the neural mechanism underlying panic and to screen potential anti-panic agents. Predator-elicited flight responses, e.g., confrontation of a mouse by a snake (Griebel et al., 1996; Uribe-Mariño et al., 2012) and exposure to ultrasound in rats (Beckett et al., 1996; Klein et al., 2010) both induce panic-like flight behaviour and autonomic changes characteristic of panic. The elevated T-maze has been validated as a sensitive behavioural test that can discriminate between panic-like and anxiety-like behaviour in rats and mice (Graeff et al., 1998; Teixeira et al., 2000; Pobbe et al., 2011). The mouse defense test battery is another powerful tool in this respect (Blanchard et al., 2001). In rats, disinhibition of neuronal activity in the dorsomedial hypothalamus induced by microinjection of a $GABA_A$ antagonist is a procedure that has been shown to render animals panic prone. Indeed, the panic-prone rat exhibits many of the characteristics of panic patients in that it responds with fearful behaviour and autonomic arousal to chemical panicogenic challenges that do not provoke a response in normal rats (Johnson and Shekhar, 2012; Johnson et al., 2008).

2.2. PAG and panic

Whilst there is much merit in these models, perhaps the most translational model of panic in animals, which equates directly with the human condition, is the response evoked by stimulation in the dorsal part of the midbrain periaqueductal grey matter (PAG). More than 40 years ago neurosurgeons investigating deep brain stimulation at midbrain sites as a method for relieving intractable pain reported that the procedure often evoked intolerable side effects, which resembled the symptoms of panic (Kumar et al., 1997; Nashold et al., 1969; Richardson and Akil, 1977). As a consequence this procedure was soon abandoned. However, in terms of understanding the neural basis of panic, the experience of those pain patients was important since it validated stimulation in the dorsal part of the PAG as a panic model in animals. In rats dorsal PAG stimulation evokes flight behaviour and autonomic changes characteristic of panic (Yardley and Hilton, 1986). Animals find the stimulation highly aversive; rats readily learn to carry out tasks that will terminate the stimulus (switch-off behaviour) (Jenck et al., 1995). In rats experimental provocation of panic by inhalation of hypercarbic gas leads to functional activation of neurones in the dorsal part of the PAG (Johnson et al., 2011). In humans too, imaging studies have demonstrated activation