Hormones and Behavior 76 (2015) 106–117

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Sex differences in anxiety disorders: Interactions between fear, stress, and gonadal hormones

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ARTICLE INFO

Available online 14 April 2015

Keywords:
Sex difference
Anxiety
Fear extinction
Fear conditioning
PTSD
Estrogen
Testosterone
Progesterone
Stress
Psychiatric disorders

ABSTRACT

This article is part of a Special Issue "SBN 2014".

Women are more vulnerable to stress- and fear-based disorders, such as anxiety and post-traumatic stress disorder. Despite the growing literature on this topic, the neural basis of these sex differences remains unclear, and the findings appear inconsistent. The neurobiological mechanisms of fear and stress in learning and memory processes have been extensively studied, and the crosstalk between these systems is beginning to explain the disproportionate incidence and differences in symptomatology and remission within these psychopathologies. In this review, we discuss the intersect between stress and fear mechanisms and their modulation by gonadal hormones and discuss the relevance of this information to sex differences in anxiety and fear-based disorders. Understanding these converging influences is imperative to the development of more effective, individualized treatments that take sex and hormones into account.

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Introduction

Women are twice as likely as men to develop stress- and anxiety-related psychiatric disorders (Kessler et al., 1995, 2006, 2009; Tolin and Foa, 2006). This sex bias may be attributed in part to a greater sensitivity to stressful and traumatic life experiences in women. Indeed, numerous studies have examined sex differences in the response to stress and have identified differences in the neural circuits that impact emotional reactivity (Goldstein et al., 2010; Kogler et al., 2014). However, how these mechanisms may be mediating sex differences in anxiety disorders remains unclear. It is often observed that individuals who suffer from anxiety have great difficulty forming memories and learning new or challenging tasks. Profound sex differences have been documented in laboratory experiments, where inducing stress or fear has also led to impaired learning and memory consolidation. Therefore, investigating the mechanisms of learning and memory that are differentially affected by stress, fear, or the combination of both may provide insight into the systems that mediate these sex differences.

In this review, we focus on processes of fear regulation (acquisition and extinction) to explore these sex differences and compare the findings to what has been reported in the stress literature. As gonadal hormones, such as estrogen and testosterone, are known to influence learning and memory processes as well, these factors will be included in our discussion. By describing the intersection of stress, fear, and gonadal hormones in learning and memory modulation, we aim to promote a better understanding of the factors that increase vulnerability to anxiety disorders to potentially improve the efficacy and efficiency of treatment.

Sex differences in anxiety disorders

Anxiety disorders are the most prevalent of mental disorders, with an estimated lifetime prevalence rate of about 16% world-wide and 20% in the U.S. alone (Kessler et al., 2005, 2009). Epidemiological reports consistently indicate that women are at about a two-fold higher risk for any anxiety-related disorder compared to men (Breslau et al., 1997; Foa and Street, 2001; Kessler et al., 1994, 1995, 2005; McLean et al., 2011; Nolen-Hoeksema and Girgus, 1994; Tolin and Foa, 2006). The higher incidence rate in women is maintained across all anxiety- and fear-based disorders, including social anxiety disorder, generalized anxiety disorder, panic disorder, specific phobia, and post-traumatic stress disorder (PTSD; Breslau, 2009; Breslau et al., 1997; Kessler et al., 1994, 1995). Although PTSD and obsessive compulsive disorder (OCD) are no longer classified as anxiety disorders in the DSM-V, we will include them in our discussion as they share important features with anxiety disorders and were defined as such in previous DSMs.

Women seem to be more negatively affected by symptoms of anxiety disorders, often experiencing symptoms to a greater degree (Altemus et al., 2014). Women comprise more than half of the population with generalized anxiety disorder and have a greater

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http://dx.doi.org/10.1016/j.yhbeh.2015.04.002
0018-506X/Published by Elsevier Inc.

vulnerability to comorbid mental disorders that persist later in life (60 years of age and older; American Psychiatric Association, 2013; Bakish, 1999; van der Veen et al., 2014). Women are not only twice as likely to develop PTSD following a traumatic event, but they also experience more severe, debilitating, and persistent symptoms (Breslau et al., 1998; Holbrook et al., 2002; Seedat et al., 2005). In individuals with panic disorder, this increased severity of symptoms is demonstrated by women who experience a higher frequency of panic attacks than men (Kessler et al., 2006; Reed and Wittchen, 1998). These differences contribute to an overall worse quality of life for women suffering from anxiety disorders compared to men with these disorders (Breslau et al., 1998; Breslau, 2002; Frans et al., 2005; Holbrook et al., 2002; Kilpatrick et al., 2013; Perrin et al., 2014; Seedat et al., 2005). In addition to these pronounced differences in symptom severity, men and women also differentially express the characteristics and symptoms of anxiety disorders. For instance, women are more likely to show obsessive–compulsive disorder symptoms in the contamination/cleaning domain, whereas men exhibit more obsessive behaviors related to the sexual/religious dimension of OCD (Labad et al., 2008).

Epidemiological studies suggest that women may have a higher risk for developing anxiety disorders, or exacerbation of their present symptoms, during different phases of their reproductive lives, such as puberty, menses, pregnancy, postpartum, and menopause (Hickey et al., 2012; Pigott, 2003; Ross and McLean, 2006; Van Veen et al., 2009; Vesga-López et al., 2008). These periods of elevated risk coincide with times of drastic hormonal fluctuations, implicating a role for gonadal hormones in the onset, maintenance, and persistence of anxiety disorders in women. This sex-specific elevated risk for developing fear and anxiety disorders may be due to an inability to down regulate negative emotional responses to stress and fear (Campbell-Sills et al., 2006; Cover et al., 2014; Lebron-Milad and Milad, 2012; Mennin et al., 2005; Nolen-Hoeksema, 1991).

Neurobiology of fear extinction

Fear is a necessary and adaptive response that is critical for survival, but it can develop into debilitating psychopathology if it does not subside in the absence of threat. Pavlovian fear conditioning is a learning paradigm that is commonly used to investigate fear learning and memory processes. Fear learning occurs after several presentations of a neutral conditioned stimulus (CS), such as a light or tone, which is paired with an aversive unconditioned stimulus (US), such as a mild shock. The subject learns that the CS predicts the US and expresses conditioned responses (CRs) to subsequent CS presentations. The CR that is usually measured to assess fear is freezing behavior in rodents and skin conductance response (SCR) or fear-potentiated startle in humans. During fear extinction, the CS is repeatedly presented without the expected negative consequence; the subject learns that the CS no longer predicts the aversive US and exhibits a reduction in either freezing or SCR. As the neurobiology of fear extinction has been studied extensively and implicated in the etiology of anxiety and stress-related disorders (Bishop, 2007; Dias et al., 2013; Hofmann, 2008), it is not surprising that stress and fear responses are mediated by overlapping neural circuits. Here, we focus on the fear extinction network, including the ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), amygdala, and hippocampus (Linnman et al., 2011, 2012; Milad et al., 2007).

Relevance to anxiety disorders

The exaggerated fear response is a signature characteristic of anxiety- and stress-related disorders. This is especially true for individuals suffering from PTSD, who struggle to control fear elicited by stimuli associated with past traumatic events. Understanding the fear extinction network can inform research on anxiety disorders not only because of their shared neurobiology, but also because fear extinction processes model some of the core behavioral features of anxiety disorders (for review, see Graham and Milad, 2011; Maren et al., 2013; Pitman et al., 2012). These shared characteristics allow findings from the rodent fear extinction model to be easily translated to clinical applications (Briscione et al., 2014; Milad and Quirk, 2012; Norrholm et al., 2011). For instance, PTSD patients exhibit poor extinction recall, which appears to be associated with disruptions in the fear extinction network, e.g., hyperactivity within the dACC and hypoactivity within the vmPFC (Etkin and Wager, 2007; Liberzon and Sripada, 2008; Milad et al., 2009a,b; Pitman et al., 2012). Similarly, extinction recall and its neural correlates are disrupted in OCD patients (Milad et al., 2013). Although more studies are necessary to evaluate the implications of its use, the fear extinction model may be an effective transdiagnostic tool to detect susceptibility to anxiety disorders and predict recovery after a stressful life event in humans and rodents (Marin et al., 2014). In addition to identifying biomarkers of vulnerability to anxiety disorders, another potential application of this model may also be to help assess the efficacy of treatment. Prolonged exposure therapy is one of the most effective forms of cognitive behavioral therapy for the treatment of anxiety disorders (Foa, 2000, 2011; McLean and Foa, 2013). This treatment induces extinction learning by exposing the individual to the stimulus that provokes their uncontrollable fear in the absence of any negative outcomes or danger. Fear extinction may be a good experimental model for investigating the neural mechanisms that underlie these treatments and identifying the dysfunctional target areas that make some individuals less responsive to therapy.

Rodent fear circuitry

The above described fear extinction network in humans was based and driven by numerous studies conducted on rodents. In rodents, the circuit modulating fear expression involves excitatory input from the prelimbic (PL) medial prefrontal cortex (mPFC) to the basolateral amygdala (BLA), which activates the central amygdala (CeA) for enhanced fear expression (Likhtik et al., 2005; Sierra-Mercado et al., 2011; Sotres-Bayon et al., 2004). The infralimbic (IL) area of the mPFC projects to, and activates inhibitory intercalated cells in, the amygdala. These cells connect the BLA to the CeA and inhibit fear output (Likhtik et al., 2005; Quirk et al., 2003; Quirk and Mueller, 2008; Sierra-Mercado et al., 2011; Sotres-Bayon et al., 2004). The hippocampus interacts with this network in response to contextual cues and can induce or suppress fear memory expression depending on the context (Sotres-Bayon et al., 2012). For instance, the hippocampus will activate IL to suppress fear when the CS is presented in the context in which it was extinguished (Corcoran and Maren, 2001).

Human fear circuitry

The rodent circuitry for fear conditioning and extinction appears to have functional homologies with that of humans (Milad and Quirk, 2012). Neuroimaging studies illustrating brain activations during fear conditioning and extinction suggest that the human dACC and vmPFC are homologous with the rodent PL and IL, respectively (Fig. 1; Linnman et al., 2011, 2012). Extinction memory recall (as indicated by low SCR to the CS) was positively associated with increased activation of the vmPFC during presentation of the extinguished CS (Kalisch et al., 2006; Milad et al., 2007; Phelps et al., 2004). In addition, the amygdala and hippocampus were also activated during these tasks, demonstrating similar functional roles as in rodents (Kalisch et al., 2006).