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REVIEW

THE INFLUENCE OF STRESS AT PUBERTY ON MOOD AND LEARNING: ROLE OF THE $\alpha_4\beta\delta$ GABA$_A$ RECEPTOR

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Abstract—It is well-known that the onset of puberty is associated with changes in mood as well as cognition. Stress can have an impact on these outcomes, which in many cases, can be more influential in females, suggesting that gender differences exist. The adolescent period is a vulnerable time for the onset of certain psychopathologies, including anxiety disorders, depression and eating disorders, which are also more prevalent in females. One factor which may contribute to stress-triggered anxiety at puberty is the GABA$_A$ receptor (GABAR), which is known to play a pivotal role in anxiety. Expression of $\alpha_4\beta\delta$ GABARs increases on the dendrites of CA1 pyramidal cells at the onset of puberty in the hippocampus, part of the limbic circuitry which governs emotion. This receptor is a sensitive target for the stress steroid 3α-OH-5[α]β-pregnan-20-one or [allo]pregnanolone, which paradoxically reduces inhibition and increases anxiety during the pubertal period (post-natal day ~35–44) of female mice in contrast to its usual effect to enhance inhibition and reduce anxiety. Spatial learning and synaptic plasticity are also adversely impacted at puberty, likely a result of increased expression of $\alpha_4\beta\delta$ GABARs on the dendritic spines of CA1 hippocampal pyramidal cells, which are essential for consolidation of memory. This review will focus on the role of these receptors in mediating behavioral changes at puberty. Stress-mediated changes in mood and cognition in early adolescence may have relevance for the expression of psychopathologies in adulthood.

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Key words: puberty, GABA-A receptor, alpha4, delta, anxiety, cognition.

Contents

INTRODUCTION

It is well known that adolescence is a period frequently associated with behavioral and cognitive changes in humans, which can include mood swings (Buchanan et al., 1992), increased/altered response to stress (Susman et al., 1988; Modesti et al., 2006), risk-seeking

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Abbreviations: 3α-HSD, 3α-hydroxysteroid oxidoreductase; ABA, activity-based animal model of anorexia nervosa; BDNF, brain-derived neurotrophic factor; CRH, corticotrophin-releasing hormone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; E_2, 17β-estradiol (an estrogen); EPSC/EPSP, excitatory post-synaptic current/potential; ER, estrogen receptor; fMRI, functional magnetic resonance imaging; GABAR, GABA$_A$ receptor; KCC2, K^+-Cl^- co-transporter; LTP, long-term potentiation; NKCC1, Na^+-K^+-Cl^- co-transporter; NMDA, N-methyl-D-aspartate; P, progesterone; PMDD, premenstrual dysphoric disorder; PND, post-natal day; PVN, paraventricular nucleus (hypothalamus); SIG, silver-intensified gold; T, testosterone; TBS, theta-burst stimulation; TEA, tetra-ethylammonium; THDOC, 3α,21-dihydroxy-5α-pregnan-20-one; THP, 3α-OH-5[α]β-pregnan-20-one or [allo]pregnanolone; TTX, tetrodotoxin.

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behavior (Liang et al., 1995), altered social interaction, and, in some cases, decreases in CNS plasticity and cognition (Johnson and Newport, 1989; McGivern et al., 2002). It is also recognized as a particularly vulnerable time for the onset of certain psychiatric disorders, including generalized anxiety disorder (Reardon et al., 2009) and depression (Heim et al., 2004), which are more prevalent in females (Dorn and Chrousos, 1997), as well as a period when stress can influence the eventual development of some psychiatric disorders, such as schizophrenia, that occur later in adulthood (Dahl, 2004; Corcoran et al., 2012). Some studies have noted developmental milestones associated with chronological age which impact upon some of these cognitive and behavioral outcomes (Vetter-O'Hagen and Spear, 2012). However, the onset of puberty is associated with an array of hormonal events which converge to produce viable reproductive function. These same hormonal events may also contribute to some of the psychological and cognitive changes associated with puberty which are not directly linked to reproductive function.

Stress is defined as the body's reaction to environmental demands which elicit physical, mental or emotional responses, in most cases correlated with changes in heart rate and/or blood pressure. Most studies typically use performance stress (oral presentations, mental arithmetic, mirror tracing, etc.) for human stress evaluations and restraint stress or CO_2 inhalation for rodent studies. Stress steroids are steroids released as part of the reaction to stress. The most well-known stress hormones include epinephrine, norepinephrine and corticosterone; Animal studies have shown that corticosterone, in particular, produces profound effects on mood and cognition via acute and chronic effects on neuronal function and viability (McEwen, 2007; Davidson and McEwen, 2012; McEwen et al., 2012). However, this article will focus on the role of 3α-OH-5[α]β-pregnan-20-one or [allo]pregnanolone (THP) in mediating some of the changes in mood and cognition observed during the pubertal period. THP is also a steroid released by stress (Purdy et al., 1991; Higashi et al., 2005; Girdler et al., 2006), by the adrenal and CNS in both humans and rodents, which functions to modulate inhibition via direct effects on the $GABA_A$ receptor (GABAR), a receptor shown to play a pivotal role in anxiety (Rudolph et al., 1999; Trincavelli et al., 2012) in mice and humans.

ANXIETY AND ADOLESCENCE

One of the most prevalent types of psychopathologies in human adolescents is anxiety (Costello et al., 2003). In fact, anxiety disorders with a lifetime course are most likely to begin at the time of puberty. In one study the median age of onset was 11 years (Kessler et al., 2005), consistent with pubertal onset, with more than 50% having an onset by age 14, during the pubertal period. There are also gender differences in psychopathology during adolescence, with girls more likely to develop an anxiety disorder (Hayward and Sanborn, 2002), for whom the most common subtypes reported are social anxiety and panic disorder (Zgourides and Warren, 1988; Costello et al., 2003). Both the prevalence and intensity of panic attacks have been correlated with pubertal status in girls (Hayward et al., 1992; Leen-Feldner et al., 2007).

STRESS AND ADOLESCENCE

Response to a stressful experience is increased at the onset of puberty (Susman et al., 1988; Modesti et al., 2006; Sumter et al., 2010; Lui et al., 2012), where performance on a video game was shown to provoke increases in blood pressure, and the anticipatory stress of public speaking increased cortisol responses in adolescents to a greater degree than in younger children. Puberty is also widely regarded as the onset of gender differences in negative affect as a response to stress (Dorn and Chrousos, 1997; Ordaz and Luna, 2012). Many studies in humans have reported greater negative mood in females in early adolescence as a response to performance or psychosocial stressors (Garber et al., 2002; Ge et al., 2010), which is a trait that can extend into adulthood (Kelly et al., 2008). In studies investigating the autonomic changes triggered by stressors (mental arithmetic, mirror tracing, interpersonal stress) in early to mid-adolescence, females responded with a greater increase in heart rate compared to their male adolescent counterparts (Matthews et al., 1990; Ewart and Kolodner, 1991; Syme et al., 2009). Anxiety responses to acute stressful stimuli are also correlated with the more advanced pubertal Tanner stages in females (Huerta and Brizuela-Gamino, 2002; Leen-Feldner et al., 2007). In addition to the response to acute stress, the response to chronic stress is exacerbated in adolescence: in individuals experiencing post-traumatic stress disorder, puberty onset was associated with an increase in negative affect, re-experience and hyperarousal (Carrion et al., 2002). Stress during adolescence can lead to different coping mechanisms, which may either be palliative or result in dysfunctional behavior, including risk-taking behavior and substance abuse.

Regional activity is increased in an age and gender-specific fashion throughout the cortico-limbic circuit which is involved in the stress response during adolescence. This includes the amygdala, hippocampus, insula and hypothalamus. Functional magnetic resonance imaging (fMRI) has been used to assess such activity during a psychosocial stress paradigm (Guyer et al., 2009). In females, increased activity of the hypothalamus, insula, nucleus accumbens and hippocampus was observed during the stressor, an effect correlated with age. In contrast, for males, the stressor was associated with decreased insula activity, but no change in any of the other structures. Surprisingly, there was no change in amygdala activity during the task.

There are also gender differences in the size of these structures which are correlated with the onset of puberty, when amygdala volumes are greater in males, while hippocampal volumes are greater in females (Neufang