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Review article

Adolescent vulnerability to cardiovascular consequences of chronic emotional stress: Review and perspectives for future research

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ABSTRACT

Emotional stress has been recognized as a modifiable risk factor for cardiovascular diseases. Adolescence has been proposed as a developmental period of vulnerability to stress. This idea has been mainly supported by experimental research in animals demonstrating a higher impact of chronic emotional stress in adolescents compared with adults. Adolescent vulnerability is also based on evidence that stress during this developmental period affects development, so that enduring changes are found in adult animals that experienced stress during adolescence. The purpose of the present review is to discuss experimental research in rodent models that investigated the impact of long-term exposure to stressful events during adolescence on cardiovascular function. The development of cardiovascular function and autonomic activity in rodents is initially reviewed. Then, a discussion of an adolescent vulnerability to cardiovascular effects of chronic stress is presented. From the reviewed literature, perspective for future research is proposed to better elucidate adolescent vulnerability to cardiovascular complications evoked by chronic emotional stress.

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1. Introduction

Convergent clinical and preclinical evidence has shown an important role of psychosocial factors (e.g., environmental and social stresses, anxiety, mood states, and personality traits) in the etiology and progression of several cardiovascular dysfunctions (Carnevali et al., 2013a; Ford et al., 1998; Friedman and Rosenman, 1959; Grippo and Johnson, 2009; Kawachi et al., 1994;

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Roest et al., 2010; Rosenman et al., 1975; Rozanski et al., 1999; Rugulies, 2002; Sgoifo et al., 2014; Smith et al., 2004). Among several psychosocial factors, emotional stress has been recognized as a modifiable risk factor for cardiovascular diseases (Inoue, 2014; Steptoe and Kivimaki, 2012; von Kanel, 2012). Indeed, epidemiological results and experimental data on humans and animals have demonstrated the influence of psychosocial stress on cardiovascular health (Grippo and Johnson, 2009; Jarczok et al., 2013; Kivimaki et al., 2006; Rosengren et al., 2004; Sgoifo et al., 2014; Steptoe and Kivimaki, 2012). The association between stress and cardiovascular diseases has been shown to be independent of traditional cardiovascular risk factors such as age, sex, smoking, diabetes mellitus, and obesity (Kivimaki et al., 2006; Rosengren et al., 2004; Steptoe and Kivimaki, 2012); and is observed in individuals with or without cardiovascular diseases (Rosengren et al., 2004).

The impact of stress on physiological and psychological processes is determined by individual characteristics. Indeed, it has been proposed that some phases of development may be periods of vulnerability to stress (Eiland and Romeo, 2013; McCormick et al., 2010; Spear, 2000). In this regard, results obtained in rodents have indicated adolescence as a developmental period of vulnerability to the effects of stress (Andersen and Teicher, 2008; Cruz et al., 2016; Dahl, 2004; Doremus-Fitzwater et al., 2009; Duarte et al., 2015a; Jankord et al., 2011; Stone and Quartermain, 1997). For instance, reduction in body weight gain, adrenal hypertrophy, and thymic involution induced by chronic stressors are more frequently observed in adolescent than in adult animals (Doremus-Fitzwater et al., 2009; Duarte et al., 2015a; Jankord et al., 2011; Stone and Quartermain, 1997). The impact of stress in the hypothalamus–pituitary–adrenal (HPA) axis has also supported the idea of an adolescent vulnerability. Studies directly comparing adult and adolescent animals demonstrated that only the latter presented increased basal concentrations of plasma corticosterone following exposure to chronic stressors (Duarte et al., 2015a; Jankord et al., 2011). In addition, the habituation process of the corticosterone response that is normally observed in adult animals upon repeated exposure to the same stressor (i.e., homotypic stressor) is reduced during adolescence (Doremus-Fitzwater et al., 2009; Lui et al., 2012; Romeo et al., 2006a), which may indicate reduced coping strategies during this developmental period.

The enduring effects in adulthood of stress that occurred during adolescence are also currently a matter of debate. For instance, chronic stress experience during adolescence increased anxiety-like behaviors in adulthood (Ilin and Richter-Levin, 2009; Maslova et al., 2010; Maslova et al., 2002b; Pohl et al., 2007; Schmidt et al., 2007; Sterlemann et al., 2008; Tsoory et al., 2007; Vidal et al., 2007; Wright et al., 2008). Evidence of depressive behavior in adult animals that were subjected to chronic stress in adolescence is less consistent (Maslova et al., 2010; Mathews et al., 2008; Pohl et al., 2007). Although controversial (Ariza Traslavina et al., 2014; Maslova et al., 2010; Mathews et al., 2008; McCormick et al., 2008), an increased basal and stress-induced plasma corticosterone concentration has also been observed in adult animals subjected to chronic stress during adolescence (Duarte et al., 2015a; Ilin and Richter-Levin, 2009; Pohl et al., 2007; Schmidt et al., 2007; Uys et al., 2006).

The purpose of the present review is to discuss experimental research in animal models that investigated adolescent vulnerability to cardiovascular changes evoked by long-term exposure to emotional stressful events (i.e., chronic emotional stress). The first and second sections discuss the definition of adolescent period in rodents and the development of cardiovascular function and autonomic activity in rodents, respectively. The third section then focuses on providing a review of the impact of long-term exposure to stressful events during adolescence on cardiovascular function. Differences between adolescents and adults in the immediate effects of chronic stress as well as the enduring cardiovascular effects in adulthood of stress that occurred during adolescence are discussed. The last section discusses a perspective for future research regarding the influence of development in cardiovascular complications evoked by chronic emotional stress.

2. Adolescent period in rodents

Similar with humans, adolescence in rodents is a transitional period from the dependent phase in childhood to the independent period in adulthood (McCormick et al., 2010; Spear, 2000). "Infancy" in both rats and mice has been proposed as the period of parental care from birth until weaning, which generally occurs at postnatal day (PND) 21 in the lab (Eiland and Romeo, 2013; Tirelli et al., 2003). This period is often referred to as the neonatal or preweaning phase (Eiland and Romeo, 2013), although some authors use "neonatal" to refer to the first postnatal week (Tirelli et al., 2003).

Adolescence has been proposed in both rats and mice to cover the period between the weaning and PND59 (McCormick et al., 2010; Tirelli et al., 2003). Some authors have considered the period between PND21 and PND30 as a "prepubertal phase", so that adolescence would comprise the period between PND30 and PND59 (Eiland and Romeo, 2013). More conservative classification considered adolescence as the ontogenic period from PND28 to PND42 (Spear, 2000; Spear and Brake, 1983). Nevertheless, by convention, rats and mice are considered adults at PND60, when they achieve physical and sexual maturity (Eiland and Romeo, 2013; McCormick et al., 2010; Tirelli et al., 2003).

It is beyond the scope of the present review to describe all characteristics of the rodents during adolescence. Several excellent reviews have discussed in detail the behavioral/neurobiological and physiological characteristics of rodents during this developmental period (Andersen, 2003; Casey et al., 2008; Eiland and Romeo, 2013; McCormick et al., 2010; Spear, 2000; Spear and Brake, 1983; Tirelli et al., 2003). Relevant to the present review is evidence of differences in stress-evoked physiological responses in adolescent versus adult animals. For instance, extended adrenocorticotrophic hormone (ACTH) and corticosterone responses have been documented in adolescent rodents relative to adults (Goldman et al., 1973; Romeo et al., 2006b, 2004a,b; Vazquez and Akil, 1993), and an adult-like pattern develops between PND30-PND60 (Foilb et al., 2011). Additionally, Fig. 1 shows similar arterial pressure and heart rate (HR) increases during an acute session of stress in 49-, 70-, and 80-days-old rats, indicating that cardiovascular responsivity to stress is also completely developed before 60 days of age.

As discussed below, the pattern of autonomic activity and cardiovascular function during adolescence is relevant to the evaluation of vulnerability to cardiovascular effects of chronic emotional stress during this developmental period. Therefore, before discussing the impact of chronic stress during adolescence on cardiovascular function, a detailed description of the ontogeny of cardiovascular function and autonomic activity is provided.

3. Development of cardiovascular function

Developmental characteristics of some biological systems in animal models of adolescence are relatively well described in the literature. Regarding stress systems, numerous reports have described developmental differences during adolescence in hypothalamic–pituitary–adrenal (HPA) axis responsiveness to stress (Foilb et al., 2011; Romeo et al., 2006a, 2007) as well as the ongoing development of limbic regions in the brain involved in the integration of stress responses (Andersen and Teicher, 2004; Giedd