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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.



**Contents**



## 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

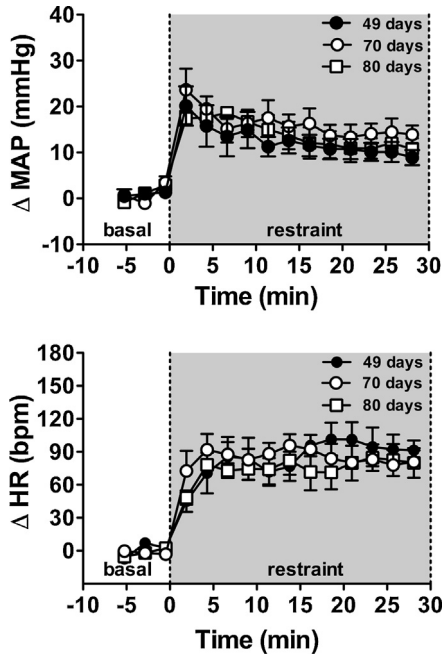


**Fig. 1.** Time course of changes in mean arterial pressure (ΔMAP) and heart rate (ΔHR) induced by an acute session of 30 min of restraint stress in male Wistar rats at PND49, PND70, and PND80. Twenty-four hours before assessment of restraint-evoked cardiovascular changes, animals were subjected to surgical preparation under anesthesia with tribromoethanol (250 mg/kg, i.p.) for implantation of catheter into the abdominal aorta through the femoral artery for cardiovascular recording. In the trial day, cardiovascular recording began at least 30 min before the onset of the restraint, and was performed throughout the session of restraint. Shaded area indicates the period of restraint. Circles represent the mean and bars the SEM. Note that cardiovascular responses to restraint stress were not significantly different during adolescence (PND49) and adulthood (PND70 and PND80).

et al., 1999; Gogtay et al., 2004; Isgor et al., 2004; Meyer et al., 1978; Romeo and Sisk, 2001). The development of cardiovascular function has also been extensively evaluated. As stated above and discussed in details below, the pattern of autonomic activity and cardiovascular function during adolescence is relevant to the evaluation of vulnerability to cardiovascular effects of stress during this developmental period. Therefore, before discussing the cardiovascular responses to chronic stress in adolescence, discussion of the development of cardiovascular function and autonomic activity in rodents is provided. The primary focus is to discuss the development during the adolescence. However, a complete description of the development of cardiovascular function in rodents from birth until adulthood is provided in order to provide a better understanding of the development pattern during adolescence in relation to complete ontogeny. A schematic representation sketching the complete development of HR, arterial pressure, sympathetic and parasympathetic activity, and baroreflex activity from birth until adulthood is presented in Fig. 2.

### 3.1. Sympathetic and parasympathetic activity

In the second postnatal day, a functional sympathetic control of the heart is identified (Kirby and McCarty, 1987; Lau and Slotkin, 1981) and the HR is already under the tonic influence of sympathetic activity (Tucker, 1985; Tucker and Domino, 1988). A decrease in sympathetic neural control of HR has been reported from PND8-PND10 to PND20-PND24 (Kasparov and Paton, 1997; Tucker, 1985; Tucker and Domino, 1988). However, adrenal gland and sympathetic innervation of the heart are immature in this developmental period (Bareis and Slotkin, 1980; Slotkin, 1973; Yamada et al., 1980). Therefore, decrease of sympathetic neural control of cardiac activity during the preweaning period seems to be mediated mainly by changes in the sensitivity of cardiac tissue to catecholamine. In fact, the density of cardiac $\beta_1$-adrenoceptor peaks at the third day after the birth and then declines to adult levels (Chen et al., 1979). Consistent with this result, during the first days following birth, a fast increase in maximal HR response to electrical stimulation of the sympathetic nerve and isoproterenol treatment is observed (Adolph, 1967).

Recent studies demonstrated that adolescent rats presented augmented sympathetic tone of the heart (Duarte et al., 2015a,b). In addition to providing evidence of a role of increased sympathetic activity in elevated baseline HR during adolescence, this result indicates that the decrease in sympathetic control of cardiac function observed during the pre-weaning period continues during adolescence.

Less information is available regarding the development of sympathetic control of arterial pressure. Results of the arterial pressure response to tyramine, an indirectly acting sympathomimetic amine, and the α-adrenoceptor agonist methoxamine have evidenced a progressive increase of the pressor response to these agents from birth until the PND40 (Smith et al., 1984). Considering that the tyramine response reflects the presence of vascular sympathetic nerve terminals containing sufficient noradrenaline to activate α-adrenoceptor in vascular smooth muscle, whereas methoxamine directly activates postsynaptic α-adrenoceptor, these results suggest that the development of sympathetic nerve terminals innervating the vascular smooth muscle develop parallel to postsynaptic receptors until PND40. However, it was demonstrated that by PND10-PND12 sympathetic post-ganglionic nerve activity was comparable to that of adults (Smith et al., 1982). Therefore, it is possible that vascular sympathetic innervation matures early, and progressive increases in pressor response to tyramine and methoxamine reflect the slower development of post-synaptic α-adrenoceptors. Indeed, a progressive increase in the number of α-adrenoceptor in peripheral tissues (e.g., lung, kidney, and liver) is observed during pre-weaning period, reaching adult values by PND30 to PND50 (McCaughran et al., 1986; Slotkin et al., 1986). These findings are consistent with the data discussed in the next section demonstrating that arterial pressure increases during the pre-weaning period (Bartolome et al., 1980; Kasparov and Paton, 1997), but values are adult-like by PND25 (Canese et al., 2009; Cruz et al., 2016; Duarte et al., 2015a,b; Kasparov and Paton, 1997). In fact, recently, we reported similar sympathetic vasomotor modulation at PND38 and PND70 (Duarte et al., 2015b). Additionally, the pressor response to a selective $\alpha_1$-adrenoceptor agonist was similar in adolescent and adult animals (Cruz et al., 2016; Duarte et al., 2015a).

Tonic parasympathetic control of HR first appears between PND10 and PND20 (Adolph, 1967; Kasparov and Paton, 1997; Tucker and Johnson, 1984). As stated above, cardiac activity is under tonic control of sympathetic activity in the first days following birth (Adolph, 1967; Tucker, 1985; Tucker and Domino, 1988). Therefore, during the first postnatal week, HR seems to be controlled primarily by the sympathetic nervous system (Adolph, 1967; Tucker, 1985; Tucker and Domino, 1988).

Although a cardiac parasympathetic tone is identified only at the second postnatal week, a decrease in HR following electrical stimulation of the peripheral end of the vagus nerve is already observed at the first day after birth (Mills, 1978). Furthermore, muscarinic cholinergic receptors were identified in the atrium and ventricle of 5-days-old rat hearts (McCaughran et al., 1987). These results indicate the presence of a functional parasympathetic innervation to the heart despite the absence of basal cardiac parasympathetic tone. Supporting this idea, Kasparov and Paton (1997) demonstrated that vagally-mediated reflex bradycardia is functional in the first week after birth. Recent studies did not report differences

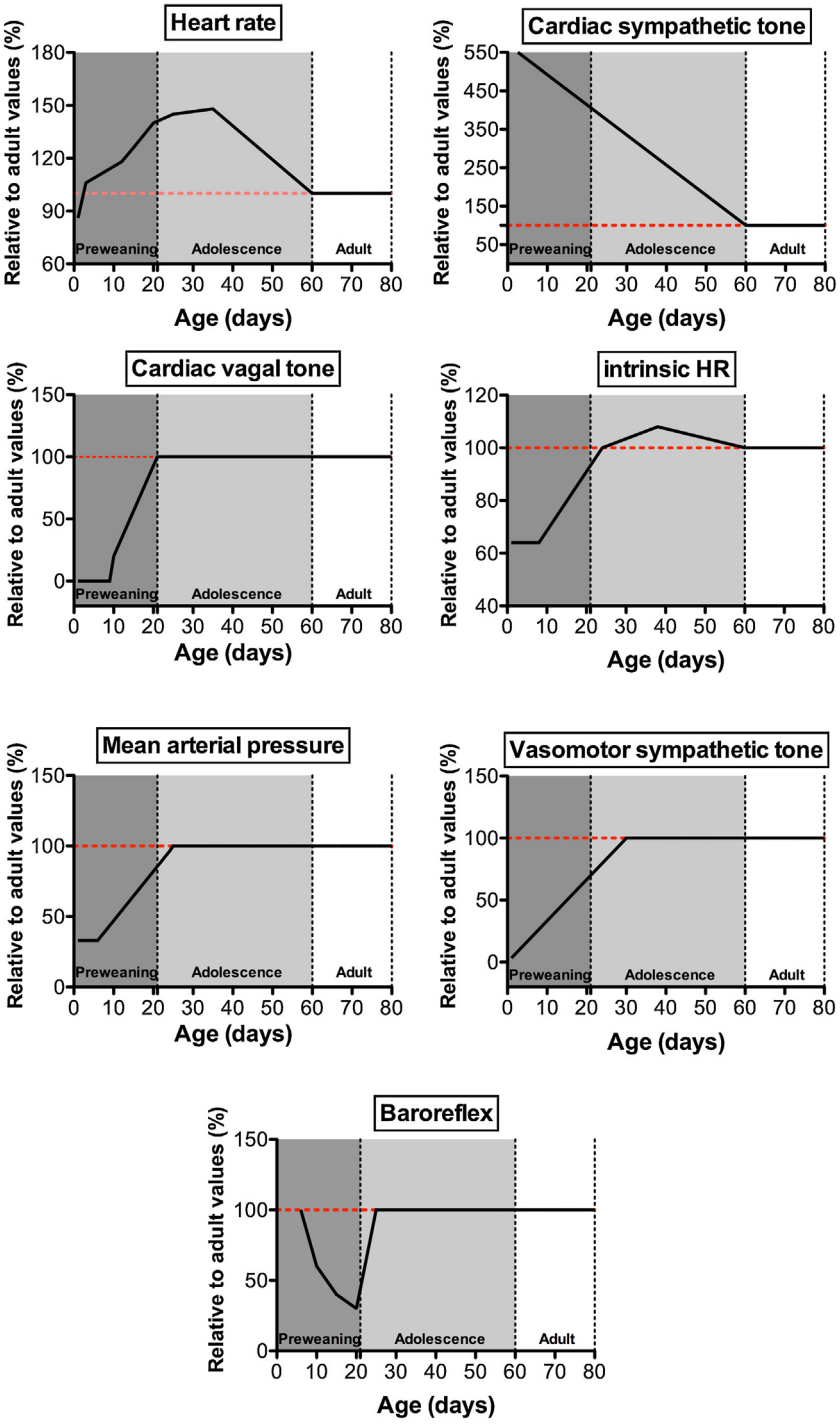


**Fig. 2.** Schematic representation illustrating the development of mean arterial pressure, heart rate, pacemaker activity of the sinoatrial node (intrinsic HR), cardiac vagal and sympathetic tone, vasomotor sympathetic tone, and baroreflex function from birth until adulthood. Representation is relative to values in adulthood, which is indicated by the dashed red line. For details, see text of Section 3.

between adolescent and adult animals in cardiac parasympathetic activity (Duarte et al., 2015a; Duarte et al., 2015b), indicating that the vagal tone of the heart seems to be adult-like by weanling.

### 3.2. Heart rate and arterial pressure

Basal values of HR increase non-linearly during the pre-weaning period (Adolph, 1967; Kasparov and Paton, 1997; Mills, 1978; Wekstein, 1965) until between PND25 and PND40 (Adolph, 1967; Porter et al., 2004). However, studies have demonstrated that during adolescence animals exhibit greater HR than in adulthood (PND > 60) (Canese et al., 2009; Duarte et al., 2015a,b; Ristuccia and Spear, 2008a,b), indicating that values reach a peak during adolescence before completing development (see Fig. 2). Elevated HR values were observed in studies using adolescent animals with age ranging from 28 to 43 days (Canese et al., 2009; Duarte et al., 2015a,b; Ristuccia and Spear, 2008a,b).

The pacemaker activity of the sinoatrial node, referred to as the intrinsic HR, also increases during the pre-weaning period (Adolph, 1967; Kasparov and Paton, 1997; Tucker and Domino, 1988).

Similar with basal HR, adolescent rats exhibit greater values of intrinsic HR than adults (Duarte et al., 2015a), indicating that cardiac pacemaker activity also reaches a peak during adolescence (Fig. 2). Therefore, the development of sinoatrial node pacemaker activity seems to parallel the development of basal HR. In fact, the increase in intrinsic HR seems to be the main mechanism involved in the development of baseline HR during the pre-weaning period once cardiac sympathetic activity decreases and parasympathetic tone to the heart increases during this developmental period (Fig. 2) (for details, see Section 3.1). Additionally, recent results demonstrated that increased intrinsic HR, together with a higher sympathetic tone of the heart, contributes to elevated HR values during adolescence (Duarte et al., 2015a).

Regarding the development of arterial pressure, studies have indicated a progressive increase in arterial pressure values from PND6 to PND8 until between PND20 and PND25 (Bartolome et al., 1980; Kasparov and Paton, 1997). Nevertheless, contrary to HR, arterial pressure evaluated in adolescent animals did not differ from those identified in adulthood (Canese et al., 2009; Cruz et al., 2016; Duarte et al., 2015a,b), thus suggesting that this cardiovascular parameter is completely developed by the weanling.

### 3.3. Baroreflex function

The baroreflex function is an important mechanism for the regulation of arterial pressure. This cardiovascular reflex mechanism is also involved in tonic maintenance of autonomic activity (Grassi et al., 2004). Little information is available regarding the development of the baroreflex activity. The limited information indicates that reflex HR responses to either increases or decreases in arterial pressure are present at PND6 (Kasparov and Paton, 1997). However, baroreflex function underwent attenuation between PND10 and PND20 (Kasparov and Paton, 1997). Adult-like values of baroreflex function were detected at PND25 (Kasparov and Paton, 1997). A study reported that reflex HR responses to hypotension were observed only after the second postnatal week (Bartolome et al., 1980). However, in this study the evaluation of baroreflex function began at PND8, a period during which the baroreflex activity is likely to be reduced (Kasparov and Paton, 1997).

Cardiac baroreflex function does not change during adolescence. For instance, recent results demonstrated similar reflex HR responses to arterial pressure at PND38, PND49, PND60, PND70, and PND81 (Cruz et al., 2016; Duarte et al., 2015a). Analysis of spontaneous baroreflex sensitivity (i.e., evaluation of the baroreflex function over the physiological range of fluctuations in arterial pressure without any pharmacological manipulations) also did not indicate differences in baroreflex function during adolescence (Duarte et al., 2015b).

All studies investigating the development of the baroreflex function evaluated the reflex control of HR. However, reflex responses of HR and sympathetic nerve activity to arterial pressure changes may be modulated differently (Grippo et al., 2008; Miki and Yoshimoto, 2013). Furthermore, the existence of discrete subgroups of neuronal networks within the baroreflex pathway has been proposed; these allow differential modification of baroreflex control of selected sympathetic nerve outputs (Miki and Yoshimoto, 2013). Therefore, further studies are necessary to elucidate the development of reflex sympathetic nerve activity responses.

## 4. Cardiovascular responses to chronic stress in adolescence

There has been less investigation of chronic stress and cardiovascular function during adolescence compared with evidence of the impact in behavioral responses, somatic parameters, and HPA axis function. Evidence of stress effects on cardiovascular function of adolescent animals was initially obtained in studies using animal models of chronic social bond disruptions. Indeed, the effect of stress during adolescence on cardiovascular function was first described by Hallback (1975), who observed that spontaneous hypertensive rats (SHR, a genetic model of hypertension) that were reared in isolation after weaning presented reduced development of hypertension, although the blood pressure of normotensive animals was not affected by chronic social isolation (Hallback, 1975). This finding contrasts with data published later, which consistently demonstrated that social isolation during adolescence increased basal values of arterial pressure in normotensive animals (Cruz et al., 2016; Maslova et al., 2010; Shen and Ingenito, 1999). This effect was observed after either 7 (Shen and Ingenito, 1999), 21 (Cruz et al., 2016), or 42 days (Maslova et al., 2010) of social isolation, thus indicating that mild hypertension evoked by chronic social isolation is independent of the length of the protocol. Cruz et al. (2016) reported recently that the increase on arterial pressure evoked by social isolation in adolescent animals was followed by an increase in both baroreflex sensitivity and vascular reactivity to vasodilator agents. Impairment of baroreflex function and vascular responsivity to vasodilator agents has been proposed as important physiopathological mechanisms of hypertension (Grassi et al., 2006; Honzikova and Fiser, 2009; Tang and Vanhoutte, 2010). Therefore, alterations in vascular reactivity to vasodilator agents and baroreflex function may constitute important adaptive responses that oppose other alterations contributing to arterial pressure elevation, thus reducing the impact of chronic social isolation on arterial pressure.

Cardiovascular function changes have also been documented in animal models following exposure to psychological stress during adolescence. For instance, recent findings from our group demonstrated that exposure to a chronic variable stress (CVS) protocol (i.e., chronic heterotypic stressor in which animals are exposed to a variety of stressors in an unpredictable schedule in order to reduce habituation) for 10 days increased arterial pressure and HR, decreased parasympathetic and increased sympathetic tones of the heart, increased vascular reactivity to vasoconstrictor agents, and caused baroreflex changes in Wistar adolescent rats (Duarte et al., 2015a,b). These findings contrast with results reported by Maslova et al. (2002a), who did not identify changes on arterial pressure in Wistar adolescent rats and inherited stress-induced arterial hypertension (ISIAH, a rat strain with stress-dependent arterial hypertension) adolescent rats following 12 days of exposure to a CVS protocol. The discrepancy could be the result of methodological differences. For example, chronic stress was realized before the weaning in Maslova et al. (2002a), indicating that mother care may have buffered the cardiovascular effects of stress. Moreover, contrary to cardiovascular recording in conscious animals using a direct method in our studies, Maslova et al. (2002a) measured arterial pressure in animals under anesthesia using a tail-cuff method (indirect). The method used to assess arterial pressure has been proposed as an important factor affecting the evaluation of hypertension induced by chronic emotional stress (Nalivaiko, 2011). However, after extensive literature review, Nalivaiko (2011) concluded that hypertension was mainly observed in studies that measured arterial pressure using tail-cuff method. An influence of anesthesia has never been considered in stress-evoked cardiovascular changes. Nevertheless, since anesthesia may affect cardiovascular function and autonomic activity (Fluckiger et al., 1985; Shimokawa et al., 1998), discrepancy is probably related to condition in which experiment was conducted (anesthetized versus unanesthetized) rather than the method used to measure arterial pressure.

Cardiovascular changes were also observed after exposure to psychological homotypic stressors (i.e., repeated exposure to the

same stressor). Despite the absence of changes on basal values of either arterial pressure or HR, exposure to homotypic stressors during adolescence decreased the intrinsic HR and cardiac parasympathetic activity (that in turn shifted the cardiac sympathovagal balance toward sympathetic predominance), increased the vascular response to vasoconstrictor agents, and decreased vascular reactivity to vasodilator substances (Duarte et al., 2015a,b). These responses were followed by facilitation of the baroreflex bradycardiac response (Duarte et al., 2015a; Porter et al., 2004). As stated above, impairment in baroreflex function has been implicated in hypertension physiopathology (Grassi et al., 2006; Honzikova and Fiser, 2009). Therefore, improvement in baroreflex function may constitute a compensatory mechanism counteracting the other alterations that contribute to an arterial pressure elevation, thus avoiding the emergence and development of an increase in arterial pressure.

### 4.1. Studies directly comparing adolescent and adult animals

The results discussed above clearly demonstrate the impact on cardiovascular function of chronic stress during adolescence. However, most studies that were discussed above evaluated the cardiovascular effects of chronic stress only in adolescent animals. Indeed, a possible vulnerability during adolescence evidenced by directly comparing cardiovascular changes in adolescent and adult animals was addressed only recently. Table 1 summarizes the findings documented by studies that directly compared cardiovascular responses to chronic stressors in adolescent and adult animals (Cruz et al., 2016; Duarte et al., 2015a). A review of these studies indicates that a possible adolescent vulnerability to the cardiovascular changes evoked by chronic stress seems to be dependent on the chronic stress paradigm. For instance, a study evaluating the impact of chronic homotypic (repeated restraint stress-RRS) and heterotypic (CVS) psychological stressors found that the homotypic stressor shifted the sympathovagal balance toward sympathetic predominance while both stressors increased vascular reactivity to a vasoconstrictor agent selectively in adolescent animals (Duarte et al., 2015a). Additionally, despite the higher sympathetic activity and elevated basal HR during adolescence (see Section 3 for details), CVS caused a further increase in HR of adolescents via a reduction of vagal activity (Duarte et al., 2015a). However, apart from some age-specific changes, both chronic psychological stressors also evoked significant cardiovascular changes in adult animals (e.g., mild hypertension, resting tachycardia, increase in sympathetic activity, baroreflex changes, and alterations in vascular reactivity to vasodilator agents) (Duarte et al., 2015a), thus refuting the idea of adolescent vulnerability.

Adolescent vulnerability to cardiovascular effects of chronic stress was more clearly evidenced in a study that used the animal model of chronic disruption of social bonds (Cruz et al., 2016) (see Table 1). This study reported that 3 weeks of social isolation evoked cardiovascular and autonomic changes more frequently in adolescent compared with adult rats. The only changes identified in adult animals were an increase in diastolic arterial pressure and a reduction in systolic arterial pressure, which in turn reduced the pulse pressure (Cruz et al., 2016). However, chronic social isolation increased the mean arterial pressure in adolescent but not adult animals (Cruz et al., 2016). Furthermore, changes in baroreflex function and vascular reactivity to vasoactive agents were identified selectively in adolescent animals, thus supporting the idea of an adolescent vulnerability. These results are consistent with previous results demonstrating that behavioral changes associated with chronic social isolation are fully observed only if disruption of social bonds is realized during adolescence (Ferdman et al., 2007; Schenk et al., 1990; Wilkinson et al., 1994). Adolescence is a period of high social contact that in turn contributes to development (Buwalda et al., 2011; Spear, 2000), which can explain the vulnerability to effects of social isolation during this developmental period.

The studies reviewed provide initial evidence that adolescent vulnerability to cardiovascular effects of stress is rather observed in animal models of social stress than psychological stress. However, reduction in body weight gain, adrenal hypertrophy, and thymic involution induced by chronic psychological stressors (either homotypic or heterotypic) were more frequently observed in adolescents than adults (Doremus-Fitzwater et al., 2009; Duarte et al., 2015a; Jankord et al., 2011; Stone and Quartermain, 1997). An increase in basal levels of plasma corticosterone was also observed selectively in adolescent animals following exposure to chronic psychological stressors (Duarte et al., 2015a; Jankord et al., 2011). In addition, the habituation process of the corticosterone response upon repeated exposure to restraint stress (psychological stressor) is reduced during adolescence (Doremus-Fitzwater et al., 2009; Lui et al., 2012; Romeo et al., 2006a). These results indicate an adolescent vulnerability to somatic and some neuroendocrine effects of psychological stressors. Taken together with studies that evaluated the cardiovascular effects, these works indicate that a developmental vulnerability is a characteristic specific for some physiological systems rather than a general body response. Regardless, as discussed in the next section, more studies are necessary before a conclusive characterization of adolescent vulnerability to cardiovascular effects resulting from social versus psychological stressors.

### 4.2. Enduring cardiovascular effects of stress during adolescence

The idea of an adolescent vulnerability has also been based in evidence that stress during this developmental period affects development, so that enduring behavioral and neuroendocrine changes and neuroplasticity are found in adult animals that experienced stress during adolescence (Duarte et al., 2015a; Ilin and Richter-Levin, 2009; Maslova et al., 2010, 2002b; Pohl et al., 2007; Schmidt et al., 2007; Sterlemann et al., 2008; Tsoory et al., 2007; Uys et al., 2006; Vidal et al., 2007; Wright et al., 2008). Maslova et al. (2010) was the first to report enduring cardiovascular effects in adulthood of chronic stress exposure during adolescence. They found an increase in arterial pressure measured under anesthesia by the tail-cuff method in adult animals (133-days-old) that experienced either social isolation or social instability (constant rotation of partners) from PND21 to PND63 (6 weeks) (Maslova et al., 2010). This finding is in contrast with a recent study reporting absence of changes in baseline arterial pressure and HR measured by a direct method in unanesthetized adult animals (69-days-old) that were subjected to social isolation from PND28 to PND48 (3 weeks) (Cruz et al., 2016). The discrepancy may be the result of methodological differences, such as the duration of the social isolation protocol (3 weeks versus 6 weeks), method of arterial pressure measurement (direct versus indirect) (see discussion in Section 4 for details), and age of evaluation of cardiovascular function (69- versus 133-day-old).

Despite the absence of changes in basal values of arterial pressure and HR, Cruz et al. (2016) identified an increase in the reflex bradycardiac response evoked by a blood pressure increase in adult animals subjected to chronic social isolation during adolescence. Considering the involvement of the impairment of baroreflex sensitivity in the pathogenesis of hypertension (Grassi et al., 2006; Honzikova and Fiser, 2009), facilitation of reflex bradycardia may be an important mechanism avoiding an arterial pressure elevation in adult animals subjected to social isolation during adolescence.

The possible influence of chronic psychological stressors during adolescence in cardiovascular function in adulthood was also reported. However, analysis of arterial pressure, HR, cardiac autonomic activity, baroreflex function, and vascular reactivity to vasoactive agents did not reveal an influence in adulthood

**Table 1**
Summary of the findings in studies directly comparing cardiovascular responses to chronic emotional stress in adolescent and adult animals.

| | | Adolescent | | | Adult | | |
|---|---|---|---|---|---|---|---|
| | | RRS[a] | CVS[a] | Isolation[b] | RRS[a] | CVS[a] | isolation[b] |
| Cardiovascular baseline | | | | | | | |
| | Mean arterial pressure | – | ↑ | ↑ | ↑ | ↑ | – |
| | HR[c] | – | ↑ | – | – | ↑ | – |
| Autonomic activity | | | | | | | |
| | Cardiac sympathetic activity[c] | – | – | Not reported | – | ↑ | Not reported |
| | Cardiac vagal activity | ↓ | ↓ | Not reported | – | – | Not reported |
| | Intrinsic HR[c] | ↓ | – | Not reported | – | – | Not reported |
| | Baroreflex bradycardia | ↑ | ↑ | ↑ | – | ↓ | – |
| | Baroreflex tachycardia | – | ↓ | ↑ | ↑ | ↑ | – |
| Vascular function | | | | | | | |
| | Pressor response to phenylephrine | ↑ | ↑ | – | – | – | – |
| | Depressor effect of acetylcholine | ↓ | – | ↑ | ↓ | – | – |
| | Depressor effect of Sodium nitroprusside | – | – | – | ↓ | – | – |

RRS—repeated restraint stress (psychological homotypic stressor), CVS—chronic variable stress (psychological heterotypic stressor), isolation—chronic social isolation (social stressor).
Up or down arrows indicate significant increase or decrease, respectively.
[a] Duarte et al. (2015a).
[b] Cruz et al. (2016).
[c] Age difference in control groups (for details, see session "*Ontogeny of cardiovascular function*").

of the exposure to either homotypic or heterotypic stressors during adolescence (Duarte et al., 2015a,b). Power spectral analysis of the pulse interval indicated an augmentation in power of oscillatory component at low (sympathetic-related) and high (parasympathetic-related) frequencies, but the cardiac sympathovagal balance (LF/HF ratio) and basal HR were not affected (Duarte et al., 2015b). These findings are consistent with the results of Maslova et al. (2002a), who reported that the arterial pressure of adult animals (210-days-old) measured by the tail-cuff method was not affected by exposure to either CVS or repeated handling from PND21 to PND32.

Taken together, the studies that were discussed above provide evidence of minimal cardiovascular consequences in adulthood of chronic stress during adolescence, with some studies even demonstrating compensatory cardiovascular changes that avoid the emergence and development of hypertension. These results contradict the idea of adolescent vulnerability. However, investigation of enduring cardiovascular effects in adulthood of stress during adolescence is only beginning to be investigated. Therefore, as discussed in the next session, a possible adolescent vulnerability evidenced by enduring cardiovascular effects in adulthood deserves further investigation before more conclusive observations.

## 5. Perspective for future research

Studies directly comparing adolescent and adult animals provided evidence that an adolescent vulnerability to cardiovascular effects of chronic stress was more clearly observed following exposure to chronic social isolation when compared with animal models of chronic psychological stress such as RRS and CVS (Cruz et al., 2016; Duarte et al., 2015a). However, a remaining question is whether adolescent vulnerability is restrict to social isolation or is observed following exposure to other animal models of chronic social stress. In this way, further studies directly comparing the impact of other chronic social stressors (e.g., social defeat) on the cardiovascular function of adolescent and adult animals will help to address the initial idea that an adolescent vulnerability to cardiovascular effects of chronic stress is more evident in animal models of social versus psychological stress.

The studies that were reviewed above indicate minimal cardiovascular consequences in adulthood of chronic stress during adolescence. However, an important unanswered question is the possible impact of chronic emotional stress during adulthood in animals that experienced stress during adolescence. In this regard, important neuroplasticity has been reported in the limbic systems of adult animals that were stressed during adolescence (Leussis et al., 2008; Toth et al., 2008; Uys et al., 2008, 2006; Watt et al., 2009), which can affect the ability to cope with stress in adulthood. Indeed, studies have reported that stressful events in adulthood evoked greater behavioral changes in animals with a history of stress during adolescence (Avital and Richter-Levin, 2005; Tsoory et al., 2007). Therefore, an investigation of the impact of chronic stress on cardiovascular function of adult animals that were subjected to chronic stress during adolescence is necessary for a complete evaluation of a possible adolescent vulnerability evidenced by enduring cardiovascular effects in adulthood.

As discussed above, increased sympathetic tone to the heart is observed in adolescent animals relative to adult animals (Duarte et al., 2015a,b). Several sympathetic-related cardiac complications have been reported in adult animals following exposure to chronic stressors, including changes in the electrical conduction system of the heart, left and right ventricular hypertrophy, arrhythmias, and cardiac contractile dysfunctions (Bruder-Nascimento et al., 2012; Carnevali et al., 2012, 2013b; Costoli et al., 2004; Duarte et al., 2015a; Grippo et al., 2006; Nagaraja and Jeganathan, 1999; Xie et al., 2012; Zhao et al., 2007). Increases in both susceptibility to cardiac arrhythmias (Grippo et al., 2012, 2004, 2010) and severity of myocardial ischemia (Mercanoglu et al., 2008; Scheuer and Mifflin, 1998) have also been reported after repeated exposure to stressful events. Thus, an increased sympathetic tone to the heart during adolescence may provide vulnerability to chronic stress-evoked cardiac complications. Therefore, comparisons in adolescent and adult animals of cardiac complications following exposure to chronic stress are relevant unvalued aspect in the determination of adolescent vulnerability.

## 6. Conclusions

The last years have brought a significant increase in research using animal models on the impact of long-term stress exposure during adolescence in cardiovascular function and autonomic activity. However, investigation of adolescent vulnerability to cardiovascular effects of chronic stress is only beginning to be

investigated, and a number of issues need to be addressed before more conclusive analysis. For instance, reviewed literature indicates that an adolescent vulnerability seems to be dependent on the chronic stress paradigm, being apparently more evident in models of social versus psychological stress. However, this idea is supported by evidence obtained in only one model of social stress (i.e., chronic social isolation). Additionally, only a limited number of studies directly compared adolescent and adult animals. In addition, despite the evidence of increased sympathetic tone to the heart in adolescent animals, the emergence of sympathetic-related cardiac complications following exposure to chronic stressors was never evaluated in adolescent animals. A review of the studies that evaluated the enduring cardiovascular changes in adulthood of chronic stress during adolescence does not support the idea of adolescent vulnerability. However, an important remaining issue is the possibility that stress during adolescence affects the ability to cope with stress during adulthood, thus resulting in greater cardiovascular complications.

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## References

Adolph, E.F., 1967. Ranges of heart rates and their regulations at various ages (rat). Am. J. Physiol. 212, 595–602.
Andersen, S.L., 2003. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci. Biobehav. Rev. 27, 3–18.
Andersen, S.L., Teicher, M.H., 2004. Delayed effects of early stress on hippocampal development. Neuropsychopharmacology 29, 1988–1993.
Andersen, S.L., Teicher, M.H., 2008. Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci. 31, 183–191.
Ariza Traslavina, G.A., de Oliveira, F.L., Franci, C.R., 2014. Early adolescent stress alters behavior and the HPA axis response in male and female adult rats: the relevance of the nature and duration of the stressor. Physiol. Behav. 133, 178–189.
Avital, A., Richter-Levin, G., 2005. Exposure to juvenile stress exacerbates the behavioural consequences of exposure to stress in the adult rat. Int. J. Neuropsychopharmacol. 8, 163–173.
Bareis, D.L., Slotkin, T.A., 1980. Maturation of sympathetic neurotransmission in the rat heart. I. Ontogeny of the synaptic vesicle uptake mechanism and correlation with development of synaptic function. Effects of neonatal methadone administration on development of synaptic vesicles. J. Pharmacol. Exp. Ther. 212, 120–125.
Bartolome, J., Mills, E., Lau, C., Slotkin, T.A., 1980. Maturation of sympathetic neurotransmission in the rat heart. V. Development of baroreceptor control of sympathetic tone. J. Pharmacol. Exp. Ther. 215, 596–600.
Bruder-Nascimento, T., Campos, D.H., Leopoldo, A.S., Lima-Leopoldo, A.P., Okoshi, K., Cordellini, S., Cicogna, A.C., 2012. Chronic stress improves the myocardial function without altering L-type Ca + 2 channel activity in rats. Arq. Bras. Cardiol. 99, 907–914.
Buwalda, B., Geerdink, M., Vidal, J., Koolhaas, J.M., 2011. Social behavior and social stress in adolescence: a focus on animal models. Neurosci. Biobehav. Rev. 35, 1713–1721.
Canese, R., Adriani, W., Marco, E.M., De Pasquale, F., Lorenzini, P., De Luca, N., Fabi, F., Podo, F., Laviola, G., 2009. Peculiar response to methylphenidate in adolescent compared to adult rats: a phMRI study. Psychopharmacology (Berl.) 203, 143–153.
Carnevali, L., Mastorci, F., Graiani, G., Razzoli, M., Trombini, M., Pico-Alfonso, M.A., Arban, R., Grippo, A.J., Quaini, F., Sgoifo, A., 2012. Social defeat and isolation induce clear signs of a depression-like state, but modest cardiac alterations in wild-type rats. Physiol. Behav. 106, 142–150.
Carnevali, L., Trombini, M., Porta, A., Montano, N., de Boer, S.F., Sgoifo, A., 2013a. Vagal withdrawal and susceptibility to cardiac arrhythmias in rats with high trait aggressiveness. PLoS One 8, e68316.
Carnevali, L., Trombini, M., Rossi, S., Graiani, G., Manghi, M., Koolhaas, J.M., Quaini, F., Macchi, E., Nalivaiko, E., Sgoifo, A., 2013b. Structural and electrical myocardial remodeling in a rodent model of depression. Psychosom. Med. 75, 42–51.
Casey, B.J., Jones, R.M., Hare, T.A., 2008. The adolescent brain. Ann. N. Y. Acad. Sci. 1124, 111–126.
Chen, F.M., Yamamura, H.I., Roeske, W.R., 1979. Ontogeny of mammalian myocardial beta-adrenergic receptors. Eur. J. Pharmacol. 58, 255–264.
Costoli, T., Bartolomucci, A., Graiani, G., Stilli, D., Laviola, G., Sgoifo, A., 2004. Effects of chronic psychosocial stress on cardiac autonomic responsiveness and myocardial structure in mice. Am. J. Physiol. Heart Circ. Physiol. 286, H2133–H2140.
Cruz, F.C., Duarte, J.O., Leao, R.M., Hummel, L.F., Planeta, C.S., Crestani, C.C., 2016. Adolescent vulnerability to cardiovascular consequences of chronic social stress: immediate and long-term effects of social isolation during adolescence. Dev. Neurobiol. 6 (1), 34–46, http://dx.doi.org/10.1002/dneu.22297.
Dahl, R.E., 2004. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. Ann. N. Y. Acad. Sci. 1021, 1–22.
Doremus-Fitzwater, T.L., Varlinskaya, E.I., Spear, L.P., 2009. Social and non-social anxiety in adolescent and adult rats after repeated restraint. Physiol. Behav. 97, 484–494.
Duarte, J.O., Cruz, F.C., Leao, R.M., Planeta, C.S., Crestani, C.C., 2015a. Stress vulnerability during adolescence: comparison of chronic stressors in adolescent and adult rats. Psychosom. Med. 77, 186–199.
Duarte, J.O., Planeta, C.S., Crestani, C.C., 2015b. Immediate and long-term effects of psychological stress during adolescence in cardiovascular function: comparison of homotypic vs heterotypic stress regimens. Int. J. Dev. Neurosci. 40, 52–59.
Eiland, L., Romeo, R.D., 2013. Stress and the developing adolescent brain. Neuroscience 249, 162–171.
Ferdman, N., Murmu, R.P., Bock, J., Braun, K., Leshem, M., 2007. Weaning age, social isolation, and gender, interact to determine adult explorative and social behavior, and dendritic and spine morphology in prefrontal cortex of rats. Behav. Brain Res. 180, 174–182.
Fluckiger, J.P., Sonnay, M., Boillat, N., Atkinson, J., 1985. Attenuation of the baroreceptor reflex by general anesthetic agents in the normotensive rat. Eur. J. Pharmacol. 109, 105–109.
Foilb, A.R., Lui, P., Romeo, R.D., 2011. The transformation of hormonal stress responses throughout puberty and adolescence. J. Endocrinol. 210, 391–398.
Ford, D.E., Mead, L.A., Chang, P.P., Cooper-Patrick, L., Wang, N.Y., Klag, M.J., 1998. Depression is a risk factor for coronary artery disease in men: the precursors study. Arch. Intern. Med. 158, 1422–1426.
Friedman, M., Rosenman, R.H., 1959. Association of specific overt behavior pattern with blood and cardiovascular findings; blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. J. Am. Med. Assoc. 169, 1286–1296.
Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. 2, 861–863.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent 3rd, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. U. S. A. 101, 8174–8179.
Goldman, L., Winget, C., Hollingshead, G.W., Levine, S., 1973. Postweaning development of negative feedback in the pituitary–adrenal system of the rat. Neuroendocrinology 12, 199–211.
Grassi, G., Seravalle, G., Dell'Oro, R., Facchini, A., Ilardo, V., Mancia, G., 2004. Sympathetic and baroreflex function in hypertensive or heart failure patients with ventricular arrhythmias. J. Hypertens. 22, 1747–1753.
Grassi, G., Trevano, F.Q., Seravalle, G., Scopelliti, F., Mancia, G., 2006. Baroreflex function in hypertension: consequences for antihypertensive therapy. Prog. Cardiovasc. Dis. 48, 407–415.
Grippo, A.J., Johnson, A.K., 2009. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 12, 1–21.
Grippo, A.J., Santos, C.M., Johnson, R.F., Beltz, T.G., Martins, J.B., Felder, R.B., Johnson, A.K., 2004. Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. Am. J. Physiol. Heart Circ. Physiol. 286, H619–H626.
Grippo, A.J., Beltz, T.G., Weiss, R.M., Johnson, A.K., 2006. The effects of chronic fluoxetine treatment on chronic mild stress-induced cardiovascular changes and anhedonia. Biol. Psychiatry 59, 309–316.
Grippo, A.J., Moffitt, J.A., Johnson, A.K., 2008. Evaluation of baroreceptor reflex function in the chronic mild stress rodent model of depression. Psychosom. Med. 70, 435–443.
Grippo, A.J., Sgoifo, A., Mastorci, F., McNeal, N., Trahanas, D.M., 2010. Cardiac dysfunction and hypothalamic activation during a social crowding stressor in prairie voles. Auton. Neurosci. 156, 44–50.
Grippo, A.J., Moffitt, J.A., Sgoifo, A., Jepson, A.J., Bates, S.L., Chandler, D.L., McNeal, N., Preihs, K., 2012. The integration of depressive behaviors and cardiac dysfunction during an operational measure of depression: investigating the role of negative social experiences in an animal model. Psychosom. Med. 74, 612–619.
Hallback, M., 1975. Consequence of social isolation on blood pressure, cardiovascular reactivity and design in spontaneously hypertensive rats. Acta Physiol. Scand. 93, 455–465.
Honzikova, N., Fiser, B., 2009. Baroreflex sensitivity and essential hypertension in adolescents. Physiol. Res. 58, 605–612.
Ilin, Y., Richter-Levin, G., 2009. Enriched environment experience overcomes learning deficits and depressive-like behavior induced by juvenile stress. PLoS One 4, e4329.
Inoue, N., 2014. Stress and atherosclerotic cardiovascular disease. J. Atheroscler. Thromb. 21, 391–401.
Isgor, C., Kabbaj, M., Akil, H., Watson, S.J., 2004. Delayed effects of chronic variable stress during peripubertal–juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. Hippocampus 14, 636–648.

Jankord, R., Solomon, M.B., Albertz, J., Flak, J.N., Zhang, R., Herman, J.P., 2011. Stress vulnerability during adolescent development in rats. Endocrinology 152, 629–638.
Jarczok, M.N., Jarczok, M., Mauss, D., Koenig, J., Li, J., Herr, R.M., Thayer, J.F., 2013. Autonomic nervous system activity and workplace stressors—a systematic review. Neurosci. Biobehav. Rev. 37, 1810–1823.
Kasparov, S., Paton, J.F., 1997. Changes in baroreceptor vagal reflex performance in the developing rat. Pflugers Arch. 434, 438–444.
Kawachi, I., Sparrow, D., Vokonas, P.S., Weiss, S.T., 1994. Symptoms of anxiety and risk of coronary heart disease. The normative aging study. Circulation 90, 2225–2229.
Kirby, R.F., McCarty, R., 1987. Ontogeny of functional sympathetic innervation to the heart and adrenal medulla in the preweanling rat. J. Auton. Nerv. Syst. 19, 67–75.
Kivimaki, M., Virtanen, M., Elovainio, M., Kouvonen, A., Vaananen, A., Vahtera, J., 2006. Work stress in the etiology of coronary heart disease—a meta-analysis. Scand. J. Work Environ. Health 32, 431–442.
Lau, C., Slotkin, T.A., 1981. Maturation of sympathetic neurotransmission in the rat heart. VII. Suppression of sympathetic responses by dexamethasone. J. Pharmacol. Exp. Ther. 216, 6–11.
Leussis, M.P., Lawson, K., Stone, K., Andersen, S.L., 2008. The enduring effects of an adolescent social stressor on synaptic density, part II: poststress reversal of synaptic loss in the cortex by adinazolam and MK-801. Synapse 62, 185–192.
Lui, P., Padow, V.A., Franco, D., Hall, B.S., Park, B., Klein, Z.A., Romeo, R.D., 2012. Divergent stress-induced neuroendocrine and behavioral responses prior to puberty. Physiol. Behav. 107, 104–111.
Maslova, L.N., Bulygina, V.V., Markel, A.L., 2002a. Chronic stress during prepubertal development: immediate and long-lasting effects on arterial blood pressure and anxiety-related behavior. Psychoneuroendocrinology 27, 549–561.
Maslova, L.N., Bulygina, V.V., Popova, N.K., 2002b. Immediate and long-lasting effects of chronic stress in the prepubertal age on the startle reflex. Physiol. Behav. 75, 217–225.
Maslova, L.N., Bulygina, V.V., Amstislavskaya, T.G., 2010. Prolonged social isolation and social instability in adolescence in rats: immediate and long-term physiological and behavioral effects. Neurosci. Behav. Physiol. 40.
Mathews, I.Z., Wilton, A., Styles, A., McCormick, C.M., 2008. Increased depressive behaviour in females and heightened corticosterone release in males to swim stress after adolescent social stress in rats. Behav. Brain Res. 190, 33–40.
McCaughran Jr., J.A., Juno, C.J., O'Malley, E., Rosenthal, M., 1986. The ontogeny of renal alpha 1- and alpha 2-adrenoceptors in the Dahl rat model of experimental hypertension. J. Auton. Nerv. Syst. 17, 1–20.
McCaughran Jr., J.A., Juno, C.J., O'Malley, E., 1987. Differential ontogeny of alpha 1-adrenergic and cholinergic receptor sites in the atria and ventricles of the inbred Dahl hypertension-sensitive (S/JR) and -resistant (R/JR) rat. J. Auton. Nerv. Syst. 20, 207–220.
McCormick, C.M., Smith, C., Mathews, I.Z., 2008. Effects of chronic social stress in adolescence on anxiety and neuroendocrine response to mild stress in male and female rats. Behav. Brain Res. 187, 228–238.
McCormick, C.M., Mathews, I.Z., Thomas, C., Waters, P., 2010. Investigations of HPA function and the enduring consequences of stressors in adolescence in animal models. Brain Cogn. 72, 73–85.
Mercanoglu, G., Safran, N., Uzun, H., Eroglu, L., 2008. Chronic emotional stress exposure increases infarct size in rats: the role of oxidative and nitrosative damage in response to sympathetic hyperactivity. Methods Find. Exp. Clin. Pharmacol. 30, 745–752.
Meyer, G., Ferres-Torres, R., Mas, M., 1978. The effects of puberty and castration on hippocampal dendritic spines of mice. A Golgi study. Brain Res. 155, 108–112.
Miki, K., Yoshimoto, M., 2013. Sympathetic nerve activity during sleep, exercise, and mental stress. Auton. Neurosci. 174, 15–20.
Mills, E., 1978. Time course for development of vagal inhibition of the heart in neonatal rats. Life Sci. 23, 2717–2720.
Nagaraja, H.S., Jeganathan, P.S., 1999. Influence of different types of stress on selected cardiovascular parameters in rats. Indian J. Physiol. Pharmacol. 43, 296–304.
Nalivaiko, E., 2011. Animal models of psychogenic cardiovascular disorders: what we can learn from them and what we cannot. Clin. Exp. Pharmacol. Physiol. 38, 115–125.
Pohl, J., Olmstead, M.C., Wynne-Edwards, K.E., Harkness, K., Menard, J.L., 2007. Repeated exposure to stress across the childhood–adolescent period alters rats' anxiety- and depression-like behaviors in adulthood: the importance of stressor type and gender. Behav. Neurosci. 121, 462–474.
Porter, J.P., Phillips, A., Rich, J., Wright, D., 2004. Effect of chronic stress on the cardiac baroreflex in the post-weanling rat. Life Sci. 75, 1595–1607.
Ristuccia, R.C., Spear, L.P., 2008a. Adolescent and adult heart rate responses to self-administered ethanol. Alcohol. Clin. Exp. Res. 32, 1807–1815.
Ristuccia, R.C., Spear, L.P., 2008b. Autonomic responses to ethanol in adolescent and adult rats: a dose-response analysis. Alcohol 42, 623–629.
Roest, A.M., Martens, E.J., de Jonge, P., Denollet, J., 2010. Anxiety and risk of incident coronary heart disease: a meta-analysis. J. Am. Coll. Cardiol. 56, 38–46.
Romeo, R.D., Sisk, C.L., 2001. Pubertal and seasonal plasticity in the amygdala. Brain Res. 889, 71–77.
Romeo, R.D., Lee, S.J., Chhua, N., McPherson, C.R., McEwen, B.S., 2004a. Testosterone cannot activate an adult-like stress response in prepubertal male rats. Neuroendocrinology 79, 125–132.
Romeo, R.D., Lee, S.J., McEwen, B.S., 2004b. Differential stress reactivity in intact and ovariectomized prepubertal and adult female rats. Neuroendocrinology 80, 387–393.
Romeo, R.D., Bellani, R., Karatsoreos, I.N., Chhua, N., Vernov, M., Conrad, C.D., McEwen, B.S., 2006a. Stress history and pubertal development interact to shape hypothalamic–pituitary–adrenal axis plasticity. Endocrinology 147, 1664–1674.
Romeo, R.D., Karatsoreos, I.N., McEwen, B.S., 2006b. Pubertal maturation and time of day differentially affect behavioral and neuroendocrine responses following an acute stressor. Horm. Behav. 50, 463–468.
Romeo, R.D., Karatsoreos, I.N., Jasnow, A.M., McEwen, B.S., 2007. Age- and stress-induced changes in corticotropin-releasing hormone mRNA expression in the paraventricular nucleus of the hypothalamus. Neuroendocrinology 85, 199–206.
Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W.A., Blackett, K.N., Sitthi-amorn, C., Sato, H., Yusuf, S., I. investigators, 2004. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 364, 953–962.
Rosenman, R.H., Brand, R.J., Jenkins, D., Friedman, M., Straus, R., Wurm, M., 1975. Coronary heart disease in Western Collaborative Group Study: final follow-up experience of 8 1/2 years. JAMA 233, 872–877.
Rozanski, A., Blumenthal, J.A., Kaplan, J., 1999. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 99, 2192–2217.
Rugulies, R., 2002. Depression as a predictor for coronary heart disease. A review and meta-analysis. Am. J. Prev. Med. 23, 51–61.
Schenk, S., Gorman, K., Amit, Z., 1990. Age-dependent effects of isolation housing on the self-administration of ethanol in laboratory rats. Alcohol 7, 321–326.
Scheuer, D.A., Mifflin, S.W., 1998. Repeated intermittent stress exacerbates myocardial ischemia-reperfusion injury. Am. J. Physiol. 274, R470–R475.
Schmidt, M.V., Sterlemann, V., Ganea, K., Liebl, C., Alam, S., Harbich, D., Greetfeld, M., Uhr, M., Holsboer, F., Muller, M.B., 2007. Persistent neuroendocrine and behavioral effects of a novel, etiologically relevant mouse paradigm for chronic social stress during adolescence. Psychoneuroendocrinology 32, 417–429.
Sgoifo, A., Carnevali, L., Grippo, A.J., 2014. The socially stressed heart. Insights from studies in rodents. Neurosci. Biobehav. Rev. 39, 51–60.
Shen, S., Ingenito, A.J., 1999. Depressor effect of kappa opioid agonist on hypertension induced by isolation in the rat. Clin. Exp. Hypertens. 21, 275–297.
Shimokawa, A., Kunitake, T., Takasaki, M., Kannan, H., 1998. Differential effects of anesthetics on sympathetic nerve activity and arterial baroreceptor reflex in chronically instrumented rats. J. Auton. Nerv. Syst. 72, 46–54.
Slotkin, T.A., 1973. Maturation of the adrenal medulla. II. Content and properties of catecholamine storage vesicles of the rat. Biochem. Pharmacol. 22, 2033–2044.
Slotkin, T.A., Kavlock, R.J., Cowdery, T., Orband, L., Bartolome, M., Whitmore, W.L., Bartolome, J., 1986. Effects of neonatal methylmercury exposure on adrenergic receptor binding sites in peripheral tissues of the developing rat. Toxicology 41, 95–106.
Smith, P.G., Slotkin, T.A., Mills, E., 1982. Development of sympathetic ganglionic neurotransmission in the neonatal rat. Pre- and postganglionic nerve response to asphyxia and 2-deoxyglucose. Neuroscience 7, 501–507.
Smith, P.G., Poston, C.W., Mills, E., 1984. Ontogeny of neural and non-neural contributions to arterial blood pressure in spontaneously hypertensive rats. Hypertension 6, 54–60.
Smith, T.W., Glazer, K., Ruiz, J.M., Gallo, L.C., 2004. Hostility, anger, aggressiveness, and coronary heart disease: an interpersonal perspective on personality, emotion, and health. J. Pers. 72, 1217–1270.
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24, 417–463.
Spear, L.P., Brake, S.C., 1983. Periadolescence: age-dependent behavior and psychopharmacological responsivity in rats. Dev. Psychobiol. 16, 83–109.
Steptoe, A., Kivimaki, M., 2012. Stress and cardiovascular disease. Nat. Rev. Cardiol. 9, 360–370.
Sterlemann, V., Ganea, K., Liebl, C., Harbich, D., Alam, S., Holsboer, F., Muller, M.B., Schmidt, M.V., 2008. Long-term behavioral and neuroendocrine alterations following chronic social stress in mice: implications for stress-related disorders. Horm. Behav. 53, 386–394.
Stone, E.A., Quartermain, D., 1997. Greater behavioral effects of stress in immature as compared to mature male mice. Physiol. Behav. 63, 143–145.
Tang, E.H., Vanhoutte, P.M., 2010. Endothelial dysfunction: a strategic target in the treatment of hypertension? Pflugers Arch. 459, 995–1004.
Tirelli, E., Laviola, G., Adriani, W., 2003. Ontogenesis of behavioral sensitization and conditioned place preference induced by psychostimulants in laboratory rodents. Neurosci. Biobehav. Rev. 27, 163–178.
Toth, E., Gersner, R., Wilf-Yarkoni, A., Raizel, H., Dar, D.E., Richter-Levin, G., Levit, O., Zangen, A., 2008. Age-dependent effects of chronic stress on brain plasticity and depressive behavior. J. Neurochem. 107, 522–532.
Tsoory, M., Cohen, H., Richter-Levin, G., 2007. Juvenile stress induces a predisposition to either anxiety or depressive-like symptoms following stress in adulthood. Eur. Neuropsychopharmacol. 17, 245–256.
Tucker, D.C., 1985. Components of functional sympathetic control of heart rate in neonatal rats. Am. J. Physiol. 248, R601–R610.
Tucker, D.C., Domino, J.V., 1988. Balance among autonomic controls of heart rate in neonatal spontaneously hypertensive and borderline hypertensive rats. J. Auton. Nerv. Syst. 22, 11–21.

Tucker, D.C., Johnson, A.K., 1984. Development of autonomic control of heart rate in genetically hypertensive and normotensive rats. Am. J. Physiol. 246, R570–R577.
Uys, J.D., Marais, L., Faure, J., Prevoo, D., Swart, P., Mohammed, A.H., Stein, D.J., Daniels, W.M., 2006. Developmental trauma is associated with behavioral hyperarousal, altered HPA axis activity, and decreased hippocampal neurotrophin expression in the adult rat. Ann. N. Y. Acad. Sci. 1071, 542–546.
Uys, J.D., Hattingh, S.M., Stein, D.J., Daniels, W.M., 2008. Large scale hippocampal cellular distress may explain the behavioral consequences of repetitive traumatic experiences—a proteomic approach. Neurochem. Res. 33, 1724–1734.
Vazquez, D.M., Akil, H., 1993. Pituitary–adrenal response to ether vapor in the weanling animal: characterization of the inhibitory effect of glucocorticoids on adrenocorticotropin secretion. Pediatr. Res. 34, 646–653.
Vidal, J., Bie, J., Granneman, R.A., Wallinga, A.E., Koolhaas, J.M., Buwalda, B., 2007. Social stress during adolescence in Wistar rats induces social anxiety in adulthood without affecting brain monoaminergic content and activity. Physiol. Behav. 92, 824–830.
von Kanel, R., 2012. Psychosocial stress and cardiovascular risk: current opinion. Swiss Med. Wkly. 142, w13502.
Watt, M.J., Burke, A.R., Renner, K.J., Forster, G.L., 2009. Adolescent male rats exposed to social defeat exhibit altered anxiety behavior and limbic monoamines as adults. Behav. Neurosci. 123, 564–576.
Wekstein, D.R., 1965. Heart rate of the preweanling rat and its autonomic control. Am. J. Physiol. 208, 1259–1262.
Wilkinson, L.S., Killcross, S.S., Humby, T., Hall, F.S., Geyer, M.A., Robbins, T.W., 1994. Social isolation in the rat produces developmentally specific deficits in prepulse inhibition of the acoustic startle response without disrupting latent inhibition. Neuropsychopharmacology 10, 61–72.
Wright, L.D., Hebert, K.E., Perrot-Sinal, T.S., 2008. Periadolescent stress exposure exerts long-term effects on adult stress responding and expression of prefrontal dopamine receptors in male and female rats. Psychoneuroendocrinology 33, 130–142.
Xie, F., Sun, L., Su, X., Wang, Y., Liu, J., Zhang, R., Wang, N., Zhao, J., Ban, T., Niu, H., Ai, J., 2012. Neuropeptide Y reverses chronic stress-induced baroreflex hypersensitivity in rats. Cell. Physiol. Biochem. 29, 463–474.
Yamada, S., Yamamura, H.I., Roeske, W.R., 1980. Ontogeny of mammalian cardiac alpha 1-adrenergic receptors. Eur. J. Pharmacol. 68, 217–221.
Zhao, Y., Wang, W., Qian, L., 2007. Hsp70 may protect cardiomyocytes from stress-induced injury by inhibiting Fas-mediated apoptosis. Cell Stress Chaperones 12, 83–95.