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Review

The socially stressed heart. Insights from studies in rodents

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ABSTRACT

The existence of a close relationship between psychosocial factors and cardiovascular morbidity is not just a hypothesis anymore. Research on humans has been attempting to unravel the significance of this association by investigating psychological and social characteristics in relation to cardiovascular health. However, this research is limited by the difficulty to control and standardize for the individual social history, the impossibility to apply psychosocial stress stimuli for mere experimental purposes, as well as the long time span of cardiovascular pathogenesis in humans. Animal studies controlling for social environment and adverse social episodes since weaning allow for partially overcoming these limitations. The aim of this review is to provide an up-to-date reference of the experimental evidence so far collected on the link between psychosocial factors and cardiovascular (dys-)function in rodent species, with special emphasis on social conflict, aggressiveness and negative mood states, which have been significantly associated with increased risk of cardiovascular disease.

Contents

1. Introduction

Psychosocial risk factors can be classified into three major categories, including the social environment, personality traits, and negative affect (von Kanel, 2012). Decades of research, both clinical–epidemiological and experimental on humans and animals, have strengthened the view of a tight link between psychosocial factors and cardiovascular morbidity (Verrier and Lown, 1984; Rozanski et al., 1999; Krantz and McCeney, 2002; Costoli et al., 2004; Sgoifo et al., 2009). Factors such as anxiety and mood states, personality traits such as anger and hostility, coping strategies, socioeconomic status, acute and chronic social stressors as well as the absence of significant social support have all been shown to modulate and interfere with cardiovascular health (Van der Kooy et al., 2007; De Vogli et al., 2007; Albus, 2010; Steptoe et al., 2010). These psychosocial variables appear to be independent risk factors, as important as traditional ones (cholesterol levels, waist fat, body mass index and poor physical activity), for the onset and progression of coronary artery disease, hypertension,

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myocardial stunning, stroke and arrhythmias (Hemingway et al., 2001; Strike and Steptoe, 2004; Wittstein et al., 2005).

An intrinsic limitation of research on humans lies in the difficulty to control and standardize for the individual social history preceding laboratory or clinical assessment. In addition, the application of psychosocial stress stimuli for experimental purposes is obviously limited by ethical concerns and regulations. Finally, it is often hard to characterize the role of social factors because of the long time span of cardiovascular pathogenesis in humans. Animal studies controlling for social environment and adverse social episodes since weaning allow for partially overcoming these limitations.

Rodent models of social and psychosocial stress and the link with depression-like states will be examined in this review, in order to provide an up-to-date reference of the experimental evidence on the relationship between adverse social environment, mood disorders and cardiovascular dysfunction.

2. The importance of the social factor

The interaction with one or more members of the same species can be a significant source of stress, particularly in those species (including primates and rodents) where social organization is complex and dynamic (Sgoifo et al., 2001). In humans, the various forms of adverse social environment appear to be the most relevant stress factor for the onset and progression of stress-related disorders, both psychosomatic (such as cardiovascular pathologies) and psychological (e.g. anxiety and depression) (Bjorkqvist, 2001).

In animals, disputes for territory control, food resources and sexual partners can be harsh and frequent and may produce severe physical and psychological damage. In humans, social stress episodes do not necessarily imply overt aggressive acts, rather they usually follow verbal and psychological pathways (Pico-Alfonso et al., 2007). Nonetheless, the social competition that originates from adverse family and work environments is characterized by hostile behaviors that often represent a serious threat to physiological and psychological well-being (Lucini et al., 2002; Rozanski et al., 2005; Strike et al., 2006).

For many years, stress biologists implemented a variety of experimental paradigms with the aim of understanding the physiological and behavioral features of stress response and the mechanisms underlying stress-related disturbances. Unfortunately, the choice of a given experimental stress protocol was often driven by an anthropomorphic line of reasoning rather than relying on the behavioral biology of the animal model (Koolhaas et al., 2011). Indeed, laboratory stress procedures were used in rodents such as immobilization or electric shock that, although inducing robust physiological activations and pathophysiological consequences, bore poor biological relevance, being based on stimuli that are unlikely in the everyday life and evolutionary history of these species (Sgoifo et al., 2005). Therefore, it is not surprising that the use of highly translational, naturalistic stress models such as social conflict, subordination, and long-term social isolation has become more and more widespread in the last years.

3. The burden of social defeat

In rodents, a single episode of social defeat has a strong physiological and behavioral impact. Social defeat is obtained by means of the resident-intruder test, which consists in introducing the experimental animal in the territory of a conspecific dominant male. Defeat is the outcome of repeated attacks by the resident rat, and the declaration of subordination by the intruder is clearly detectable on the basis of characteristic behavioral patterns (Koolhaas et al., 2013).

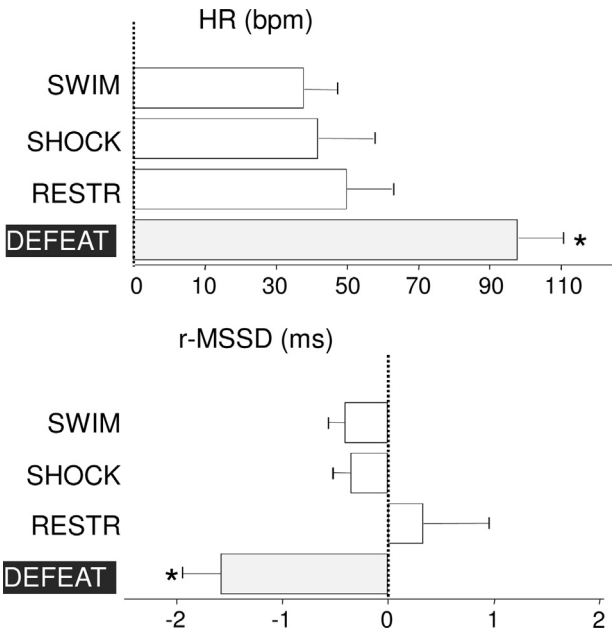

Fig. 1. Delta values (differences between 15-min test and 15-min baseline values; means ± SEM) of average heart rate (HR, bpm) and root mean square of successive R–R interval differences (r-MSSD, ms) in rats exposed to social defeat (DEFEAT), restraint test (RESTR), shock-prod test (SHOCK) and swimming test (SWIM). *DEF significantly different from all at $p < 0.05$.

In the short term (from few minutes to a few hours) defeat produces tachycardia, vagal withdrawal, cardiac arrhythmias, hypertension, hyperthermia, elevated plasma levels of glucocorticoids and catecholamines, and reduced concentrations of circulating testosterone (Sgoifo et al., 1999) (Figs. 1–3). Interestingly, 8-OH-DPAT (a 5-HT1A receptor agonist) attenuates

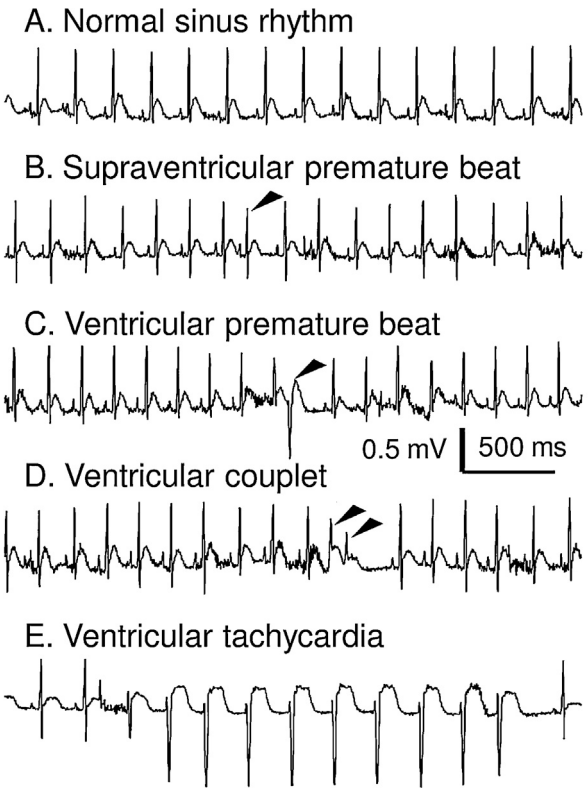

Fig. 2. Different types of tachyarrhythmias in rats exposed to social defeat test.