BORSA DI STUDIO MAESTRI DELLA SIIA 2019

Relazione prima parte del Progetto “A brain to spleen communication in stress-dependent hypertension”

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Stress is one of the most important risk factors for the pathogenesis of essential hypertension (Glaser et al., 2005; Esler et al., 2008; Sowden, 2009). Hypertension is associated with elevated circulating levels of Angiotensin II (AngII) exerting its principal effects by stimulating Angiotensin II type 1 receptors (AT1Rs) in different target organs, as the brain. More interesting, the inhibition of these receptors in specific brain regions, controlling stressful condition, promotes the dysfunctions of hypothalamic-pituitary-adrenal (HPA) axis, suggesting that the stimulation of AT1Rs drives HPA activation (Herman et al., 2008). In this stress circuit, afferent synaptic inputs converge to neurons of the paraventricular nucleus of the hypothalamus (PVN) that represents the brain station regulating in turn HPA axis outputs (Herman et al., 2008). This hypothalamic brain region, heavily influenced by psychological stress, modulates immune responses that are relevant in stress-induced hypertension (Marvar et al., 2012). Although the role of PVN neurons in stress-induced hypertension is well clear, it is completely unknown how it drives immune system in the spleen. In literature, it is reported that a stress condition promotes cardiovascular dysfunction affecting peripheral systems, principally the sympathetic nervous system (Sowden et al., 2009; Marvar and Harrison, 2012). In our previous studies we investigated the activity of splenic sympathetic nervous system in directing immune cells mobilization upon different hypertensive challenges, as AngII and DOCA-salt (Carnevale et al., 2016; Perrotta et al., 2018a and b). T cells migrated towards kidney and vasculatures that are the main districts affected by hypertension (Carnevale et al., 2014; Trott et al., 2014). More interesting, Harrison and colleagues found that repeated daily stress contributed to T cell infiltration in the aorta leading to vascular dysfunction (Marvar et al., 2010 and 2012).

The PVN controls neuroendocrine axis and the autonomic nervous system in response to physiological stress, however, neurons in the PVN that coordinate the activation of neuroendocrine axis with sympathetic outflow remains still not completely investigated. We developed transgenic mice with a selective deletion of AT1a receptors in the PVN (Agtr1aflox;Sim1Cre+/- or KO for AT1a in the PVN) and control mice (Agtr1aflox;Sim1Cre-/- or WT). These mice were obtained by crossing the conditional model for the AT1aR receptor (AT1aRflox mice) with mice expressing a Cre recombinase in specific neurons of the brain area of interest (Sim1-Cre) (de Kloet et al., 2013) and then evaluating the efficacy of the gene deletion by real-time PCR on AT1aR mRNA of the PVN of these mice. We applied an experimental protocol to induce a condition of stress, observing that mice KO for AT1a in the PVN showed not significant differences in the corticosterone (CORT) response as compared to control mice, but when we measured blood pressure, we found that the deletion of AT1a in the PVN attenuated the cardiovascular system in response to a stress condition. In particular, we observed that mice KO for AT1a receptors in the PVN had decreased blood pressure responses in terms of systolic blood pressure and a similar heart rate responses as compared to control mice. Additionally, we observed that an activation of these neurons in the PVN led to an increased activity of the sympathetic nervous system after a condition of stress, with a generalized inflammation in target organs of cardiovascular system.

Collectively, these results demonstrated that a stress condition can influence the responsiveness of neurons expressing the AT1a receptors in the PVN to conjoin the HPA axis activity with the sympathetically mediated hypertensive responses in mice.

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Date 25//11/2021 Signed

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