Autonomic Neuroscience: Basic and Clinical 185 (2014) 1–4

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

HIGHLIGHTS IN BASIC AUTONOMIC NEUROSCIENCE: INSULAR CORTEX INJURY LEADS TO CARDIOVASCULAR DYSFUNCTION

Liang Shu [a], **Yun Wang** [b,*]

[a] *Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China*
[b] *Institutes of Brain Science and State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai 200032, China*

Keywords:
Insular cortex
Cardiovascular dysfunction

Introduction

The prefrontal cortex, comprised of lateral prefrontal cortex (or insular cortex) and the medial prefrontal cortex, is involved in autonomic nervous system modulation. Insular cortex has neuronal connections with brain regions that are involved in central autonomic control, such as the hypothalamus, the nucleus of the solitary tract (NTS), and dorsal vagal nucleus and nucleus of ambiguus which contain preganglionic parasympathetic neurons. The insular cortex thus integrates sensory and visceral signals from the peripheral receptors. Recent clinical evaluation also indicates that injury of the insular cortex, by such as stroke, causes cardiovascular dysfunction. An interesting feature of the insular cortex involvement in central autonomic regulation is its differential role related to the sub-regions of the insular cortex, and particularly the lateralization of the insular cortex in terms of autonomic regulation.

Koppikar, S., Baranchuk, A., Guzmán, J.C., Morillo, C.A. (2013) Stroke and ventricular arrhythmias. Int J Cardiol. 168: 653–9.

Article summary

In this recent review article, the authors systemically reviewed the correlation between stroke and ventricular arrhythmias in several aspects including epidemiology, possible etiopathogenesis, risk factors, and clinical managements. In clinic, electrocardiographic abnormalities and cardiac arrhythmias are common features after acute stroke and the risk of malignant ventricular arrhythmias is increased after a stroke which is directly associated with sudden cardiac death. Past researchers have indicated the direct injury to neurogenic structures after stroke causes autonomic imbalance, which is the key reason to lead to myocardial damage and arrhythmogenesis. The reviewer summarized that the experimental and clinical evidences all suggest that insular cortex infarcts after stroke plays a key role in autonomic dysregulation that leads to arrhythmias in the acute setting. Experimental and clinical studies reported that insular cortical injury after stroke causes the deregulation of sympathetic/parasympathetic tones, which resulted in autonomic nervous system imbalance affecting heart rate variability and baroreflex sensitivity. Furthermore, different effects on autonomic function are considered as the outcome of insular lateralization and resulted from the augmentation of serum catecholamine levels. In this aspect, the authors suggest that, in clinic after stroke, continuous cardiac monitoring, drug therapy, and electrolyte correction may lead to risk reduction of autonomic dysfunction. However, it is urgently necessary for further studies to focus on clearly elucidating the structures of central autonomic circuit and exploring more effective management for ventricular arrhythmias after acute stroke.

Commentary

Both clinic and basic studies all suggest that the insular cortex, as a crucial part of the autonomic nervous system regulation network, is involved in regulation of the sympathetic and parasympathetic autonomic balance. Any pathological condition, such as stroke, causing injury to the insular cortex will lead to sympathetic and parasympathetic autonomic imbalance. This autonomic dysfunction can lead to reduction of heart rate variability and baroreflex sensitivity, and myocardial injury, followed by cardiac arrhythmias, ventricular fibrillation, asystole and even sudden death (Soros and Hachinski, 2012). Although increasing evidence supported insular lateralization in regulation of cardiac autonomic function, it is still under dispute. It is reported that left insular damage augmented sympathetic tone and led to lowered parasympathetic activity. In contrast, right insular injury was reported to result in sympathetic overactivity. Moreover it is still not so clear which neural pathway, the left or right insular cortex, respectively influences the control of cardiovascular autonomic function. Although this recent review article summarized the clinical and basic studies on stroke related ventricular arrhythmia and pointed out that insular cortical along with other brain structure injury may play a key role in causing this pathological condition, further studies are needed to identify neurological structures involved in autonomic control and risk factors for ventricular arrhythmogenesis after acute stroke. These studies need to pay particular attention to demonstrate the special effect of the left and right insular cortices through advanced techniques.

* Corresponding author. Tel.: +86 21 54237871; fax: +86 21 54237643.

http://dx.doi.org/10.1016/j.autneu.2014.07.001

Zhang, Z.-H., Rashba, S., Oppenheimer, S.M. (1998) Insular cortex lesions alter baroreceptor sensitivity in the urethane-anesthetized rat. Brain Research, 813: 73–81.

Article summary

In this article, the authors described a classic study on the effect of local lesion of the sub-region of the insular cortex on the baroreceptor sensitivities in anesthetized rats. By lesions of either left anterior/posterior or the same right region of insular cortex, the results showed that after right posterior insular damage, a small but significant increase was found in baseline mean artery pressure and heart rate, and only lesions of the left posterior insular cortex resulted in a significant change in baroreceptor gain. This experimental evidence, left and right insular cortices differentially modulating cardiovascular function, directly supported the hypothesis that the insular cortex has a lateralization effect on autonomic regulation. The left insular cortex can function through regulating parasympathetic activities to influence baroreflex gain, while the right insular cortex is involved with modulation of sympathetic activities.

Commentary

This early study systemically studied the relationship between the insular cortex and cardiovascular function. By using a local lesion method, they demonstrated that the left posterior insular cortex plays a key role in regulating baroreceptor gain through modulation of cardiac parasympathetic activity. On the other hand, the right posterior insular cortex lesion led to a modest but significant increase in baseline blood pressure and heart rate, while it didn't apparently affect baroreceptor gain. The former phenomenon may result from the inhibitory influence of the left posterior insular cortex on baroreceptor signals to cardiac parasympathetic neurons. The latter indicated that right insular cortex injury may increase cardiovascular sympathetic tone. Combined with the similar results obtained from some other previous researchers (Ruggiero et al., 1987; Oppenheimer and Cechetto, 1990; Oppenheimer et al., 1992), it clearly indicated that, firstly, the insular cortex is a key central brain structure with an important role in modulating cardiovascular function, secondly, the subregional part of the insular cortex plays a different role in central cardiovascular control. Most importantly, the results that the left and right insular cortices differentially modulate parasympathetic and sympathetic functions, from this study led to the hypothesis that the insular cortex has a lateralization effect on autonomic regulation. However, the mechanism of how each side of insular cortex can regulate cardiac autonomic function is still unclear. Further experiments should focus on the interaction between baroreflex activity and insular cortex function.

Toshiko Tsumori, Shigefumi Yokota, Toshiro Kishi, Yi Qin, Tatsuro Oka, Yukihiko Yasui (2006). Insular cortical and amygdaloid fibers are in contact with posterolateral hypothalamic neurons projecting to the nucleus of the solitary tract in the rat. Brain Res, 1070: 139–144.

Article summary

The authors used bilateral tracing techniques to clearly illustrate that the axons from both insular cortex and the central amygdaloid nucleus (ACe) projecting neurons, respectively, formed synaptic connections onto posterolateral hypothalamus neurons (PLH) projecting to the nucleus of the solitary tract (NST). After ipsilateral injections of tracer into either nucleus of the solitary tract or insular cortex in the rat, photomicrographs showed that nucleus of the solitary tract injected tracer CTb back-labeled neurons while BDA-labeled axon terminals after injections into the insular cortex were distributed bilaterally with an ipsilateral dominance in the PLH. The electron microscopic examination showed that the insular cortex terminals formed asymmetrical synaptic contacts with dendrites and dendritic spines of the NST-projecting PLH neurons, whereas the ACe terminals formed symmetrical synaptic contacts with somata and dendrites of the NST-projecting PLH neurons. The data from this study suggest that the central neuronal connections between insular cortex (excitatory) or central amygdaloid nucleus (inhibitory) and posterolateral hypothalamus neurons may affect cardiovascular function by regulating the activities of neurons in the nucleus of the solitary tract.

Commentary

The morphological results from this study directly indicate that both the insular cortex and central amygdaloid nucleus have connections with nucleus of the solitary tract via posterolateral hypothalamus projecting neurons. This study reported the observation of the morphological features of the connection from the insular cortical axon terminals to the posterolateral hypothalamus neurons, and then to the neurons in the nucleus of the solitary tract, which is in consistence with other previous studies (Ruggiero et al., 1987; Cechetto and Chen, 1990; Yasui et al., 1991). It suggests that the insular cortex (as well as central amygdaloid nucleus) has central connections, although indirect, with the nucleus of the solitary tract, a major nucleus located in the brain stem where peripheral autonomic signals are integrated. This result supported the functional finding that insular cortex lesions caused dysfunction of cardiovascular component. Thus, the previous and present evidences support the idea that the insular cortex — posterolateral hypothalamus — nucleus of the solitary tract neural pathway may take responsibility for regulation of cardiovascular autonomic function. Although, the recent finding (Alves et al., 2009) of the involvement of glutamatergic neurotransmission in insular cortex-evoked tonic excitatory effects on baroreflex parasympathetic activity supported the morphological evidence by electron microscopy from this study that the asymmetrical synaptic contacts from insular cortex to posterolateral hypothalamus neurons, whether there are any other neurotransmitters in this pathway and how they contribute to the effect on cardiac autonomic modulation is still unclearly explained.

Alves, F.H.F., Crestani, C.C., Resstel, L.B.M., Correa, F.M.A. (2009) Insular cortex alpha1-adrenoceptors modulate the parasympathetic component of the baroreflex in unanesthetized rats. Brain Research, 1295: 119–126.

Article summary

This study evaluated the noradrenergic neurotransmission in the insular cortex in modulating the cardiovascular reflex responses. After bilateral microinjection of the selective alpha1-adrenoceptor antagonist WB4101 into the insular cortex, the authors found augmentation of reflex bradycardia gain in response to mean arterial pressure increases triggered by intravenous phenylephrine. This effect was induced 10 min after injection and disappeared 60 min after alpha1-adrenoceptor antagonist microinjection. In contrast, this phenomenon had been observed neither after microinjection of the selective alpha2-adrenoceptor antagonist RX821002 nor after non-selective beta-adrenoceptor antagonist propranolol. Moreover, baseline mean arterial pressure and heart rate were not influenced by the injection of noradrenergic antagonists. Finally, the authors indicated that the alpha1-adrenoceptors in the insular cortex take responsibility, at least in part, for inhibitory influences on baroreflex responses to blood pressure increases.