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RESEARCH HIGHLIGHT

Finding a new job: glutamate signaling acts in atrial cardiomyocytes

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Cardiomyocytes (CMs) and neurons possess similar fundamental functions of excitability and conduction. Xie et al. provide evidence that the glutamatergic transmitter system regulating excitability and conduction in neurons is endogenously expressed and active in atrial CMs, uncovering new neuron-like signaling properties of atrial CMs.

Cardiac excitability and conduction are fundamental functions of the heart. Regulation of these functions is undeniably complex and involves multiple mechanisms including, but not limited to, autonomic nervous, nitric oxide signaling and redox balance systems. The role of the adrenergic and cholinergic nerves, part of the autonomic nervous system, in controlling cardiac electrical activity is well described and is primarily mediated by the classical neurotransmitters norepinephrine and acetylcholine. However, emerging evidence suggests that another neurotransmitter system, involving glutamate, the most abundant excitatory neurotransmitter in the nervous system, may participate in governing cardiac excitability and conduction.

Glutamate regulates excitability and conductivity of neurons in the central nervous system (CNS). Glutamate exerts its actions via binding to glutamate receptors (GluRs), which comprise ionotropic ligand-gated ion channels (iGluRs) and metabotropic G protein-coupled receptors (mGluRs). It is now recognized that, in addition to their classical localization in the CNS, GluRs are also expressed in peripheral neural and non-neural tissues including heart, kidney, lungs, ovary, testis and endocrine cells.[1] The detection of GluRs in human myocardium, in specific anatomical structures including the nerve fibers, ganglia cells, conducting system, atrial and ventricular cardiomyocytes (CMs), indicates that these receptors and the glutamatergic transmitter system may play a role in the physiology and pathophysiology of vital cardiac functions such as rhythm and excitation.[2] This idea is supported by previous studies reporting an increased incidence and inducibility of ventricular arrhythmias upon activation of the glutamatergic system. For instance, increased systemic levels of glutamate in an ischemia-reperfusion rat model and stimulation of GluRs in rats are associated with ventricular arrhythmias.[3,4] Although the mechanisms underlying arrhythmogenesis in these models remain to be fully explored, cellular and mitochondrial calcium overload, reduced protein expression of potassium channel α (Kv4.2 and Kv4.3, and Kv11.1) and β subunits (KChIP2), as well as changes in the expression and activity of the sarcoplasmic reticulum calcium ATPase (SERCA2A) have been implicated.[3, 4]

With regard to atrial arrhythmogenesis, a recent study found that glutamate signaling components are among the main gene targets of the differentially expressed microRNAs in a dog model of atrial fibrillation (AF).[5] Glutamate was also found to be increased in the left atrial appendages of patients with AF.[6] Intriguingly, a recent study by Xie et al.[7] demonstrates that elements of the glutamatergic transmitter system (e.g., glutamate metabolic enzyme, iGluRs and glutamate transporters) are expressed and functional in rat and human atrial CMs. They found that these cells show a high abundance of glutaminase, the excitatory amino acid transporter EAAT1, and the α-amino-3-hydroxy-5-methyl-4-isoxazole propionate-sensitive (AMPA) and *N*-methyl-D-aspartate (NMDA) iGluRs. Furthermore, functional experiments revealed that iGluR inhibitors and iGluR knockdown reduce conduction velocity and excitability in rat atrial myocardium and human induced pluripotent stem cell (iPSC)-derived CM monolayers, respectively, whereas iGluR activation induces iGluR-gated currents and action potentials in rat and human atrial CMs. The discovery of this functional intrinsic glutamatergic transmitter system in atrial CMs reveals a new endogenous regulatory mechanism of atrial CM excitation and conduction.

These findings point towards a potential role of the glutamatergic transmitter system in the arrhythmogenesis of atrial arrhythmias such as AF, the most common sustained cardiac rhythm disorder in man and a major source of morbidity and mortality, particularly from thromboembolic strokes. Treatment of AF remains inadequate due to insufficient understanding of AF mechanisms. Notably, Xie and colleagues showed that inhibition of iGluR with the selected blockers CNQX, MK-801 or AP-5 administered prior to AF induction reduced AF inducibility and the duration of arrhythmic episodes in a rat model of burst pacing-induced AF. Furthermore, iGluR inhibition was also effective in terminating AF after its initiation, indicating that blocking iGluRs may be sufficient to prevent arrhythmia occurrence and progression. Thus, iGluRs may represent a novel therapeutic target to prevent the onset or reduce persistence of AF.

This exciting work reveals for the first time that atrial CMs share signaling properties with glutamatergic neurons, shedding light on a new level of sophistication and complexity of atrial CM fundamental biology and identity. In combination with other non-myocyte-like properties of atrial CMs (e.g., endo-/cardio-crine[8]), this finding underscores a unique functional plasticity of these cells that is required to support vital cardiac functional properties.

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From a clinical perspective, this discovery provides insight into a novel layer of regulation of atrial CM excitability and conductivity that can potentially lead to the development of new therapeutic approaches to atrial arrhythmias like AF. Considering the wide distribution of glutamate signaling, such as in vagal afferent neurons,[9] the autonomic dysfunction consistently seen in patients with AF[10] may in part be attributed to remodeling of the glutamatergic transmitter system. Since the glutamatergic transmitter system may regulate cardiac functions other than excitation and cell-to-cell communication, like contraction and coronary circulation, altered glutamate signaling may be implicated in the pathobiology of cardiac conditions like atrial cardiomyopathy and circulatory disorders, which may need to be explored further in future work. Thus, the Xie study will undoubtedly prompt future research to explore the full impact of glutamatergic transmitter system on atrial (patho)physiology and to define the role of its dysregulation in atri0al dysfunction and arrhythmogenesis in heart disease.

Fundamentally, clarification of the multiple biological roles of GluRs and the glutamatergic transmitter system in neural and non-neural tissues, along with identification of the conditions leading to its dysregulation, will be of paramount importance in developing new therapeutic strategies targeting this multifunctional system in the heart.

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