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A Novel Neuronal Therapeutic Approach for Cardiac Arrhythmias

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Abstract

Cardiac arrhythmias, one of the leading cardiovascular diseases in young adults, has been found to lack specific therapies. Previous therapies have revolved around radiofrequency ablation, anti-arrhythmic medication, and defibrillators, which have majorly been unsuccessful in being specific and come with a variety of side effects. However, the autonomic nervous system has a significant role to play in triggering and perpetuating arrhythmias and has ample scope of targeting the agents responsible for the modulation of the cardiac wave. This review tries to include evidence of therapies that could emerge from targeting the neuronal markers and pathways in the autonomic system for arrhythmias.

Keywords: Cardiac Arrhythmias; Autonomic Nervous System; Neuronal Therapies; Atrial Fibrillation; Ventricular Fibrillation

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Introduction

Heart diseases like cardiac arrhythmias (Figure 1) are posing a major threat to healthcare departments worldwide [1]. For therapeutic targets for arrhythmias, scientists have majorly been focusing on Calcium (Ca^{2+}) dysregulation [2] for a long using different downstream and upstream agents as targets to find different approaches. Other therapies with anti-arrhythmic drugs pose different challenges since the drugs are non-tissue specific and sometimes can be pro-arrhythmic [3, 4]. Ablation-based therapies can complicate the process further posing a risk of cardiac tamponade, pulmonary vein stenosis, and other nerve injuries and traumas [5, 6]. On the other hand, an improved understanding of the autonomic nervous system has provided considerable insight into its involvement in the origin and evolution of cardiac illnesses like cardiac arrhythmias [7-9]. The cardiovascular and nervous systems work on a bi-directional feedback system mediated by the autonomic nervous system in a hierarchical form. In the hierarchy, the upper cortical centers, the brain stem, and the spinal cord make up Level 1, while the stellate and dorsal root ganglia are examples of thoracic extra-cardiac neurons at Level 2, whereas intrinsic cardiac neurons are found in Level 3 [10]. The possibilities to target the downstream and upstream processes at the neuronal level are immense.

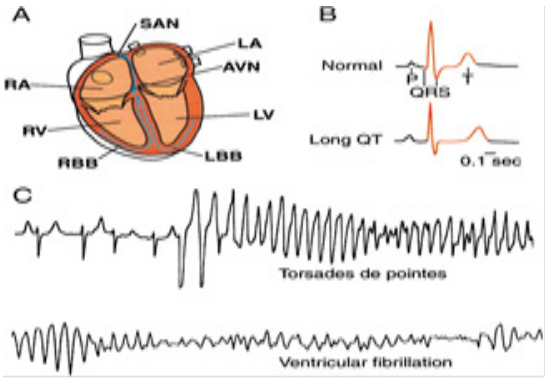

Figure 1: Molecular and cellular mechanisms of cardiac arrhythmias [1].

Possible Neural Targets in Arrhythmias

High throughput sequencing has made it possible to identify important transcripts that potentially generate proteins involved in dysfunctional neurotransmission, which allows for hypothesis testing. RNA sequencing is appropriate for examining neural reorganization of efferent and afferent neurons of the autonomic system *in vitro* because this method can be used on whole tissue as well as on individual cells.

For instance, new data suggests that defective regulation of cytosolic Ca^{2+} homeostasis and exocytosis is associated with a considerable number of differently expressed genes in stellate ganglia from hyperactive sympathetic rat models [11, 12]. The human stellate neurons in which these transcripts were maintained also offer a more comprehensive physiological viewpoint. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed to verify the differential expression of many transcripts [11]. The use of network and enrichment analysis allowed the identification of several gene ontology groupings. Extracellular ligand-gated ion

channel activity-related transcripts, particularly glutamatergic and dopaminergic signaling pathways associated with regulating Ca^{2+} balance, were identified as gene ontology families and functional pathways. Additionally, Patent Ductus Arteriosus (PDE) activity was changed, corroborating earlier studies that linked sympathetic dysautonomia to poor cyclic nucleotide signaling [11, 13].

Transcriptome alterations however offer an approach to assess the responsibility of lead genetic variants in the control of physiological processes, even though they do not immediately correspond to changes in protein levels or reveal protein-protein interactions. For instance, PDEs, which are enzymes that have selectivity for cAMP as well as cGMP, are present in cells in various isoforms and play a role in sustaining the equilibrium of cAMP and cGMP concentrations. Research has shown that the stellate ganglia in rats with sympathetic hyperactivity have a lower expression of PDE2A and PDE11A, and an increased expression of PDE6B compared to those in normal rats. However, further studies on stellate tissue from diseased rats and humans indicate that PDE2A activity and protein levels rise during times of heightened sympathetic activity [14]. When PDE2A is increased in healthy neurons through overexpression with an adenovirus, the resulting increase in PDE2A's hydrolytic activity decreases cGMP levels activated by an agonist. This mimics the diseased state and causes higher levels of Ca^{2+} and an increased release of noradrenaline from neurons [15]. It is interesting to note that in diseased neurons, cGMP activators' capacity to decrease intracellular Ca^{2+} levels and neurotransmission can be restored by inhibiting PDE2A with medication or introducing a version of PDE2A with reduced activity [14].

Whether the discovered transcripts linked to impaired sympathetic function are completely conserved throughout mammalian genomes is still up for debate. After doing an investigation, Bardsley et al. (2018) [11] revealed that the mouse stellate ganglia included several of the major transcripts thought to be candidates. Notably, the expression levels between the sexes varied significantly [16], which may need to be a consideration while researching different species. Transcriptomes offer useful data for further investigation, but they simply demonstrate a statistical relationship and make no other firm claims. It is important to confirm the transcripts at the protein level, show that they have functional importance, and show that they are present in human tissue before it can be determined whether they have an effect. This is crucial for identifying target genes and potential clinical applications.

While transcriptomics does not have any biases towards certain hypotheses, it can still uncover surprising connections that were missed using traditional pharmacological methods. Pre-synaptic beta-adrenergic receptor gene expression was found to be expressed at low levels in rats by Bardsley et al. (2018) [11] and these receptors' presence in human stellate neurons was also confirmed by qRT-PCR [17]. Studies employing animal models earlier demonstrated the presence of beta-adrenergic receptors in studies using animal models [18], and it was suggested that these receptors might be involved in regulating noradrenaline release during nerve stimulation. This idea is referred to as the "adrenaline hypothesis" of hypertension. It has recently been proven that human tissue contains beta-adrenergic receptors and the precise signaling mechanism that underlies the adrenaline theory of hypertension. Bardsley et al. (2018) [11] used RNA sequencing, immunocytochemistry, and Forster resonance energy transfer imaging to evaluate the activity of cAMP-PKA, and measurements of cytosolic Ca^{2+} concentrations to assist their findings. Only in diseased neurons did they discover a functioning Ca^{2+}-dependent exocytosis that was largely brought on by beta 2-adrenergic receptor inducement of the cAMP-PKA pathway. In an animal model of rat and human stellate neurons, increased levels of phenylethanolamine-N-methyltransferase caused messenger molecule shifting in favor of the production of adrenaline [17]. According to the research by Bardsley et al. (2018) [11] there was an upregulation in noradrenaline and adrenaline in the neuronal cells of pre-hypertensive rats. This discovery underlines the possibility that increased catecholamine release from pre-synaptic neurons could further stimulate sympathetic transmission by stimulating beta-adrenergic receptors, supporting the hypothesis that higher levels of these chemicals may contribute to the development of hypertension. Circulating catecholamines along with an increase in these chemicals' neuronal release may significantly boost cardiac postsynaptic excitability [19, 20].

The cause of heightened cardiac sympathetic transmission in heart disease is not definitively known. However, it has been observed that changes in the autonomic nervous system, both in the central and peripheral areas of the heart's neural pathway, can occur before the disease's visible signs become apparent [21-24]. Numerous studies have suggested that disruption of the NO-cGMP pathway may potentially be involved, and that oxidative stress plays a crucial role in sympathetic dysautonomia [25]. Normally, NO-cGMP stimulates PDE2A, which in turn lessens the cAMP-mediated phosphorylation of neuronal Ca^{2+}, helping to control sympathetic transmission [26-28]. In a rat model of increased sympathetic activity, boosting the protein Nos1, specifically in noradrenergic neurons, can correct issues with the NO-cGMP signaling pathway and restore normal levels of Ca^{2+}-dependent release of neurotransmitters [29, 30].

Genome-wide association studies (GWAS), which is a 'top down' approach, have offered more insight into the significance of the NO-cGMP pathway than transcriptomics, which is a 'bottom up' approach. CAPON, which is an nNOS adaptor protein also called NOS1AP has been found to have a significant influence on the modification of the NO pathway [31]. GWAS findings that single nucleotide polymorphisms in NOS1AP are connected to alterations in the QT interval and sudden cardiac mortality initially made it clear how important CAPON is to the NO-cGMP pathway [32, 33]. Additional research has revealed that polymorphisms in NOS1AP also contribute to the rise in arrhythmic incidents and sudden cardiac death in Long QT type 1 individual [34]. During NOS1AP overexpression in cardiac muscle cells, a shortening of the QT interval was noticed. It was believed that this happened via a route in which CAPON and nNOS collaborate to block ICaL and activate IKr in a cGMP-dependent manner. This causes a quicker return to the resting state, which caused the QT interval to normalize [35]. It is interesting to note that a sympathetic surge that occurs during demanding physical activity and stressful situations is a major cause of unexpected mortality in people with specific forms of LQTS [36]. CAPON was first found in the brain [37] but has also been discovered in the peripheral autonomic ganglia [31]. It has been discovered that adaptor protein upregulation in sympathetic neuronal cells lowers neurotransmission through cGMP dependent mechanism owing to the lowering of N-type Ca^{2+} current, and the Ca^{2+} transient. Mutations in CAPON may lead to aberrant sympathetic transmission and produce afterdepolarizations, while the precise role of this route in regulating arrhythmia is yet unclear.

Future Challenges

The problem with controlling the autonomic nervous system is that the most effective doses and stimulation methods are still being researched. Despite compelling preclinical data and a convincing

argument for addressing the unbalanced interaction between the sympathetic and parasympathetic neural systems in this condition, two recent studies of vagus nerve stimulation in heart failure failed to show any benefit [38].

Conclusion

Targeted therapies using neural modulation may be created when researchers obtain a greater knowledge of particular triggers responsible for different types of arrhythmias. Although the use of neural modulation for treating cardiac arrhythmias has frequently been demonstrated, it is still in its infancy or is currently being researched for other forms of arrhythmias. To verify the promising findings of earlier, smaller studies and to better understand the individual autonomic triggers, further study is required.

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