Molecular mechanisms of atrial fibrillation

Molecular mechanism of Atrial fibrillation Atrial fibrillation (AF) is a condition of the heart where the upper two chambers (atria) beat irregularly and rapidly. This condition occurs due to abnormal electrical discharge from the atria and other pulmonary nodes that cause the atria to quiver. However this is also one of the least understood of all heart conditions. Studies have been made using animals as models, analysis of the patient's family has been done to understand the genetic link and acquired form of this disease has also been studied in details. A proper and successful treatment for AF is still elusive as the molecular mechanism is not yet fully understood. Progression in the studies of genetics and molecular biology would assist in dealing with this disease in a better way. Recently studies by Chelu et al (2009) have brought into light the fact that differences in the ionic (mainly Ca 2+) current flow are responsible for causing AF and turning it into a chronic condition. As Brugada points out " Research efforts to elucidate the molecular basis of AF are focused into two main areas: human genetics and alterations in genetic expression of ion channels" (Brugada, Is Atrial fibrillation a genetic disease?: Molecular Mechanisms in Arial fibrillation).

The beating of the heart muscles, according to research, is strictly controlled by a procedure known as ' Ca 2+ induced Ca 2+ release'. Here we find that the number of Ca ions that are entering through the Cav. 1. 2 which is the L type voltage gated Ca ion channel helps in the increase of the release of more Ca ions from the sarcoplasmic reticulum through the intracellular Ca 2+ channels (ryanodine receptor type 2 or RyR2). This influx and release of Ca ions are strictly regulated by the heart muscles for the controlled beating of heart. In AF, where the atria beats rapidly, this rapid beating of the heart leads to production of more Ca ions or Calmodulin- dependent protein kinase

II (CaMKII) phosphorylation of the RyR2. In AF conditions it has also been noticed that L type voltage gated Ca ion channels show a decrease in its amplitude, so it has been deduced that this release of the Ca ions may be due to enhanced functioning of RyR2 channels. There are many reasons as to why the RyR2 channels may function differently. Earlier it was seen in researches conducted on dogs showing AF conditions, that RyR2 channels remained open in cases having low cystolic Ca ion presence. Another reason as Vest, et al, tells us from his experiments into molecular mechanisms that " SR Ca2+ leak due to RyR2 PKA hyperphosphorylation may play a role in initiation and/or maintenance of AF" (Vest, et al., Arrhythmia /electrophysiology). However further studies also reveal that this opening of RyR2 due to functional (' gain of function') problems in RyR2 channels is not the only cause that leads to AF, it may trigger the molecular basis that will create rapid atrial beating, but it is not the exclusive cause. Researches by Bhuiyan et al and Sumitomo et al have proven that certain molecular changes or mutation of the type R176Q cause an enhancement in the activity of these RyR2 channels where they fail to close completely thus leading to a leak of the Ca ions from sarcoplasmic reticulum which leads to AF conditions even in a healthy individual. Thus we find the requirement for both an arrythmogenic substrate (genetic mutation of RyR2) and a trigger to start the atrial rapid beating, to ultimately cause AF. As Chelu, et. al tell us " the single amino acid mutation in RyR2.. provides the arrythmogenic substrate ...because the mutation by itself, however, is not sufficient to initiate spontaneous AF, CaMKII most likely amplifies SR Ca 2+ leak, thus promoting atrial arrythmogenesis..."(Chelu, et. al. p. 1947).

In their recent studies Bhuiyan and Wilde pointed out " though the basic

understanding about ionic and molecular mechanisms of AF is still at the initial stage, increased inward rectifier K+ current and altered Ca2+ handling are presently thought to be the pathophysiologic basis of AF" (Bhuiyan and Wilde, p. 34). Nattel also quoted on the same lines " the molecular events leading to ionic remodeling remain incompletely understood. On the basis of evidence indicating that Ca 2+ overload has a central role in AF...."(Nattel, p. 223). So it becomes clear that more researches need to be conducted in to AF to give a better treatment to its patients. From their various researches Chelu et al came to the conclusion that by inhibiting CaMKII and also by reducing the SR Ca 2+ leak one could possibly treat AF . However it has also been seen that drugs that block Ca 2+ channel often cause the relaxation of the cardiac muscles and other antiarrhythmic drugs often lead to other life threatening conditions. As Allessie et al. points out " these ion channel changes are a response to a variety of stresses that, while contributing to the milieu favoring fibrillation, may not in and of themselves be the root cause. This observation may partially explain the limited success attained with the use of ion channel–blocking drugs in AF" (Allessie, et al., Pathophysiology and Preventation of Atrial Fibrillation). Thus for a better clinical treatment of this disease one needs a clear understanding and a detailed study into the genetic factors causing this familial disease, study of ion channels and the different ionic currents. Whatever exploration has been done on AF has helped researchers to move on from a basic level of information to a specialized clinical level of therapy. Brugada symptoms, short and long QT syndromes that cause deaths in patients, have been helped a lot from these ongoing studies. However most of these researches have been performed on animals like mice, rabbits, goats and dogs. This

may also explain the limited success on humans by these researches. Further research into the molecular mechanism and identifying the gene that triggers this condition and the mutations that go with it, will help in identifying the cause and nature of the disease. It will also help us to understand as to how this disease takes a chronic shape. Once these factors are clearly known further clinical facilities will be available providing better treatment.

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