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Cardiac arrhythmogenesis: a tale of two clocks?

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Around 3.7 million individuals worldwide die each year from cardiac arrhythmias; this exceeds the total numbers of deaths from all cancers in the Western world[1]. Despite major progress in interventional including device therapy, anti-arrhythmic medication remains central to their management. In the late 1960s Miles Vaughan Williams classified the existing drugs then used to treat cardiac arrhythmias[2,3]. This was widely adopted worldwide in both clinical management and as guidance for the development of new drugs that have saved countless lives.

However, the subsequent 50 years witnessed a heightened understanding of arrhythmic mechanisms and their biomolecular basis[4,5]. This was accompanied by discovery of the considerable number of their underlying membrane ion channel and intracellular ion transport regulatory protein molecules and characterisation of their precise roles in normal and arrhythmic activity[6]. Emerging evidence over the last two decades strongly suggests that this normal electrical function of the heart is the result of dynamic and orchestrated interactions between membrane ion channels and intracellular ion transport regulatory protein molecules within a complex molecular network[7]. These insights both enhanced our understanding of the pharmacological mechanism of actions of existing drugs and offered novel physiological targets for drug development. Yet, clinical practice may not have optimally benefitted from these advances. Arrhythmias remain a major clinical problem. Their therapy has often lagged progress in many other areas of cardiological medicine.

Might such a lack of progress reflect a lack of clarity or of organisation of these more recent and myriad findings into a coherent hypothesis that might relate fundamental physiological mechanisms to clinical therapy? Thus the Vaughan-Williams scheme had embedded such a simplified yet pragmatic working model for cardiomyocyte function in terms of then established drugs. It regarded arrhythmia as a consequence of a disruption of normal cardiac electrophysiological activation. This primarily invoked normal and abnormal function in surface membrane ion channels. It then organised these fundamental physiological mechanisms into a simple system effectively constituting what might be termed a surface membrane (M) clock (cf[8]). Individual drugs were identified with then known ion channels and their possible actions on these activation and recovery processes. Such cyclically operating system are exemplified elsewhere by the circadian rhythms ubiquitous in biological systems, in which misalignments produce negative functional effects.

Although possibly oversimplified the Vaughan-Williams scheme had provided a coherent framework for diagnostic analysis and therapeutic action, often thereby directly facilitating clinical management[9]. Any over-simplification of the actual physiological or clinical situation was mitigated by the advantages offered by its clarity and simplicity, as well as its explicit and legitimate correlations of particular therapies with then known arrhythmic targets (referenced in[7]). It has thus remained the most useful, clinically and pedagogically popular amongst classifications of anti-arrhythmic drugs (AAD). Furthermore, the few subsequent attempts to clarify these links between mechanisms of actions and therapeutic effects, exemplified by the important publication from a Working Group of the European Society of Cardiology in 1991 achieved limited success[10].

We speculate that our recent modernized Oxford classification[7] and its future developments may offer its pragmatic successor. It seeks to capture the greater proportion of both currently employed and the more recently discovered therapeutic and investigational agents. Its classification maps directly onto

the recent, important and extensive, insights and developments in cardiac electrophysiology and pharmacology. The latter have now often succeeded in identifying particular arrhythmic phenotypes with abnormalities in particular ion channels, ion transporters and signalling agents that might offer real or potential therapeutic targets at the molecular level. Embedded within it is an updated model for normal and abnormal cardiac electrophysiological activity that relates directly to its suggested classes of drug targets and their established and potential therapeutic effects (Figure 1). Thus, it added to the original M-clock, a further oscillator reflecting intracellular events contributing to cardiac activity. Many of these bear on Ca^{2+} homeostasis[11] and thus thereby come together into an additional, 'Ca^{2+} (C)-clock'. Normal cardiac excitation then requires the cyclic events in the two clocks to be aligned. Disruption in this alignment leads to arrhythmia.

Table 1 derives a simplification of the modernized Oxford classification[7] directed at drugs in current clinical use as opposed to investigational agents. It reflects its organisation in retaining but extending the original Vaughan Williams classes I-IV bearing respectively on action potential activation, autonomic action, action potential recovery and Ca^{2+} current respectively. It then adds class 0, V, VI, VII agents modifying sino-atrial automaticity, mechanosensitive and connexin associated channels, as well as upstream modulatory targets. Thus, it first incorporates the original sequential cycles of surface membrane voltage-gated Na^+ channel-mediated action potential (AP) depolarisation, and refractoriness, and K^+ channel-mediated repolarisation paced by SAN activity. However, this membrane (M-) clock is also linked to tissue level intercellular as opposed to intracellular processes that also affect action potential conduction. Pro-arrhythmic AP conduction slowing thus can follow both reduced inward Na^+ current compromising AP activation or anatomical changes altering connexin (Cx)-dependent intercellular conductances, thereby causing functionally or anatomically defined re-entrant pathways[9]. Second, it also incorporates the depolarisation-induced activation of L-type Ca^{2+} channels that produces the action potential plateau. The latter activation events are also strategic in that they *feed-forward* to the C-clock whose operation is thus normally synchronously initiated and terminated by events associated with corresponding activation and recovery events in the M-clock. Thus the resulting Ca^{2+} influx triggers ryanodine (RyR2) or inositol trisphosphate receptor-mediated SR Ca^{2+} release elevating cytosolic [Ca^{2+}]. This is terminated and reversed with repolarisation. Ca^{2+}-ATPase mediated Ca^{2+} re-uptake into the SR or Na^+-Ca^{2+} exchanger mediated expulsion into the extracellular space then restores resting cytosolic [Ca^{2+}] completing its duty cycle[11].

Arrhythmias directly result from abnormal automaticity originating from specialized conducting SAN, atrioventricular node (AVN) or Purkinje fibres, or pathological generation or conduction of excitation by atrial and ventricular cardiomyocytes, involving the M-clock. However, particular intracellular events forming the resulting intracellular C-clock *feed-back* onto specific M-clock components, with potential pro-arrhythmic consequences. Altered Ca^{2+} channel function itself may underly pro-arrhythmic, triggering, early after-depolarization (EAD) phenomena during late phase 2 or early phase 3 often of prolonged APs in common with increased late Na^+ or decreased K^+ current contributions to prolonged electrocardiographic QT intervals, resulting in electrophysiological events misaligned with and thus disturbing M-clock function. Elevated sarcoplasmic reticular [Ca^{2+}] arising from Ca^{2+} or mechanosensitive channel (MSC) activity, or increased RyR2 Ca^{2+} sensitivity, can trigger propagating waves of spontaneous SR Ca^{2+} release thus decoupling M- and C-clock activity. Thus the resulting increased cytosolic [Ca^{2+}] may transiently increase electrogenic Na^+/Ca^{2+} exchange current driving delayed after-depolarizations (DADs) following full AP repolarization[11]. It may also downregulate longer-term Na^+ channel expression and function compromising conduction. The inward depolarizing nature of Na^+/Ca^{2+} exchange also may contribute to SAN automaticity[8].

Finally, the coloured annotations match the targets identified in Figure 1 to the specific anti-arrhythmic drug classes enumerated by the modernized Oxford scheme[7]. This thus matches therapeutic strategies for anti-arrhythmic treatment to specific components of the model. We thus emerge with a new relatively simple guidance scheme relating arrhythmic mechanisms to treatment

strategies. We hope this will facilitate more effective use of what is now available whilst encouraging therapeutic advance

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Figure legend.

Figure 1: Molecular ion channel and transporter, and signalling components contributing to normal cardiac activity and arrhythmic events and their grouping (AADs 0-VII) into pharmacological targets in the updated Oxford classification scheme[7]. This scheme maps onto a two-clock scheme for normal and abnormal cardiac electrophysiological function. A membrane (M) clock mediates surface electrophysiological changes and conduction of excitation but feeds forwards onto the calcium (C-) clock through producing alterations in cytosolic Ca^{2+}. These trigger cycles of store Ca^{2+} release and re-uptake normally driven by activation and recovery processes in the M-clock. However, the C-clock also feeds back onto the M-clock, altering AP conduction, recovery, and post-recovery stability, besides exerting longer term effects on channel expression. Autonomic sympathetic and parasympathetic control mechanisms act at different control points respectively situated in the C- and M-clocks. cAMP: cyclic 3'5-adenosine monophosphate; Cx: connexin; G_i: inhibitory G protein; G_s stimulatory G-protein; HCN: hyperpolarisation-activated cyclic nucleotide-gated channel; MSC: mechanically sensitive channel; PKA: protein kinase A; RyR2: cardiac ryanodine receptor, type 2; SERCA: sarcoplasmic reticulum Ca^{2+}-ATPase; PLB: phospholamban; Na+, K+ and Ca2+ fluxes through Nav1.4, Kv and Ca1.2 channels also shown.

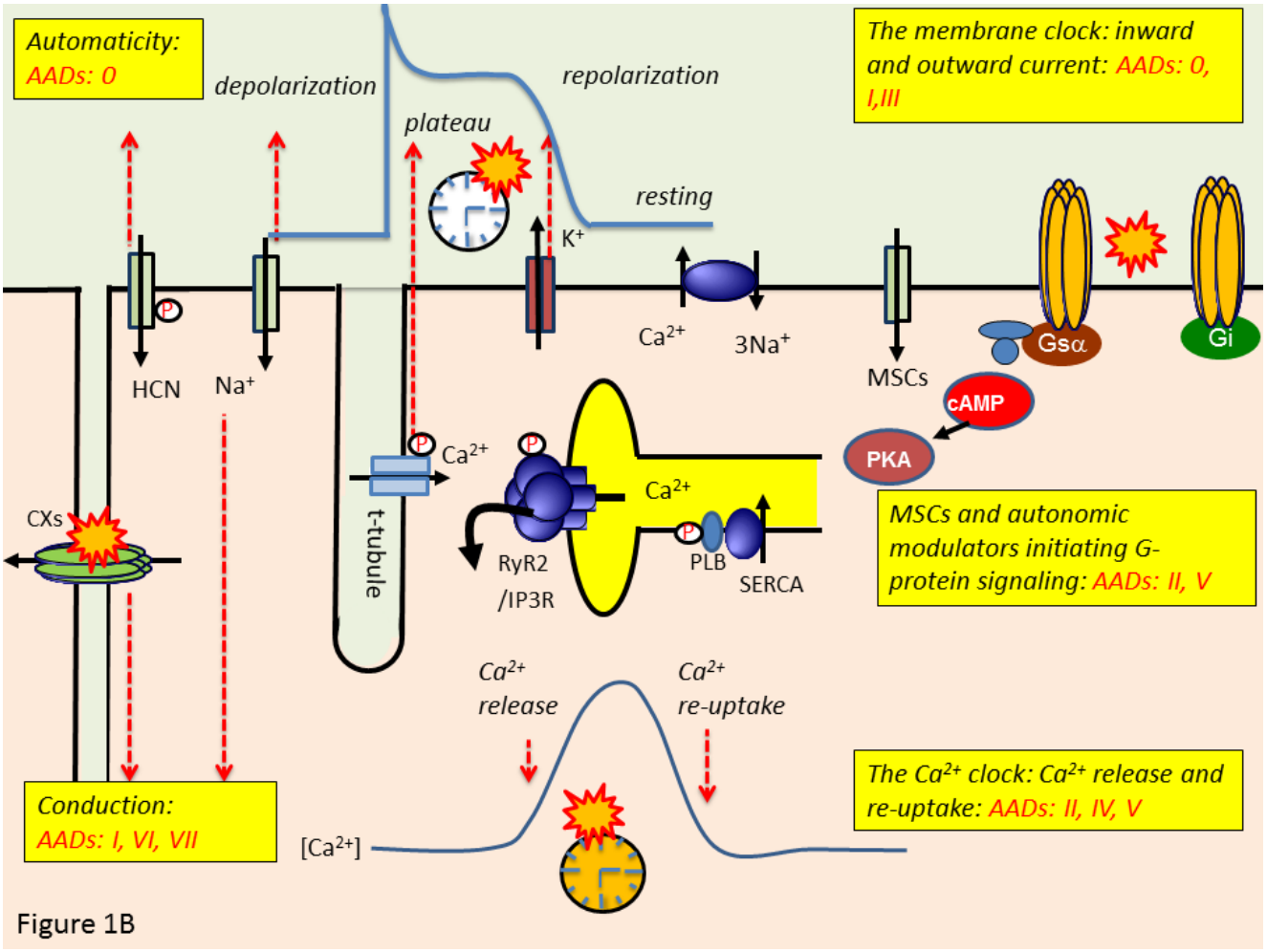

Figure 1B