Synchronising pacemakers

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Pacemaking is a property of many organs of the body. While heart pacemaking is one of the most studied there is increasing knowledge on pacemakers that drive other rhythmic activities such as brain rhythms and rhythmic contractions of smooth muscle (SM) including gastrointestinal motility, lymphatic pumping, pyeloureteric contractions, uterine contractions, vasomotion, etc.

Cellular pacemakers generally drive outcomes in an organ. These can be mediated by relatively small groups of cells that in turn drive much larger events in the organ. A primary example is the sinoatrial node pacemaker, a relatively small cellular group present in the right atrium, which activates and times the massive cardiac muscle contractions that underlie normal heartbeats. Think of a conductor directing and timing an orchestra. This *focal* pacemaker is to be contrasted to the *distributed* pacemaker present in many smooth muscles. Here the pacemaker network is distributed in parallel with or resides within smooth muscle. The primary example of the parallel network is the specialised pacemaker cell network termed interstitial Cells of Cajal (ICCs) in the gastrointestinal tract (GIT). Alternatively, the pacemaker may be within the SM cells or a sub-population of specialised SM cells.

Pacemakers undergo a rhythmical activation/relaxation cycle and hence are oscillators. It is this feature together with coupling between cells that allows pacemaker cell systems to synchronise and hence be effective. Focal and distributed pacemaker networks both require entrainment of pacemaker oscillations in each pacemaker cell. Without such entrainment there will be no net pacemaker cycle and hence no global rhythmicity. Pacemaker synchronisation in the heart and smooth muscle generally occurs through pacemaker oscillations in each cell coupling and entraining their cycling with other pacemaker cells by current flow through gap junctions that interconnect the cells. Coupling of pacemaker oscillators may also occur through cellular release of activating substances or, in the case of neurones, through synaptic interconnections. Such interactions are termed “coupled oscillators” and occur through individual oscillators being influenced by their neighbours, which enhance or impede the cycle of the oscillator and providing there is sufficient *coupling strength*, lead to entrainment. The same principle applies to the distributed pacemaker, which can also only function if there is entrainment. However over long intercellular distances involving multiple cells such as occur in the distributed pacemaker ICC network of the GIT, the entrained pacemaker cells exhibit phase delays (van Helden & Imtiaz, 2003), these being fundamental to coordinating the propulsion of gastric content. An analogy is a stadium crowd generating a “Mexican wave” that “propagates” repetitively around the stadium.

The mechanism underlying the pacemaker oscillator can vary between cell systems. The “classical” pacemaker oscillator, derived from original studies on the heart, functions through a membrane oscillator (*i.e.* the membrane clock) set by activation of cell membrane pacemaker currents, resultant action potential and ensuing hyperpolarization, the cycle then repeating (see Noble, 1984). Subsequently, another oscillator the calcium store oscillator pacemaker (*i.e.* the Ca^{2+} clock) was reported in smooth muscle (van Helden, 1993). This mechanism has since proven to underlie pacemaking in many smooth muscles (*e.g.* the GIT see van Helden & Imtiaz, 2003) and even to be a co-pacemaker in the heart (see Maltsev & Lakatta, 2009). Here the oscillator is the SR/ER Ca^{2+} store release-refill cycle with electrical transduction caused through the increase in intracellular [Ca^{2+}] at the plasma membrane opening specific ion channels. This electrical transformation markedly increases the coupling strength of the pacemaker oscillators compared to that through intercellular diffusion of Ca^{2+} or second messengers alone, so that entrainment can now occur (van Helden & Imtiaz, 2003). Neuronal pacemaking is more complicated with some rhythms known to arise through a membrane clock pacemaker but others arising through coupling of oscillatory neuronal networks.

In conclusion, cellular pacemaking occurs when the elements (*e.g.* oscillatory subcellular processes, cells or cellular networks) that underlie the pacemaker are oscillatory and coupled such that the resultant coupling strength is sufficient to allow entrainment (*e.g.* local synchronisation and possible phase waves over larger coupling distances). The resultant symphony of life in body organs, manifest as brain waves, heartbeats and rhythmic smooth muscle contractions *etc.*, remains ever intriguing.

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