Fish oils and cardioprotection – mechanisms explored

Interest in the cardioprotective properties of marine omega-3 polyunsaturated fatty acids (n-3 PUFAs) has been renewed following the publication of three large trials earlier this year demonstrating a reduction in sudden cardiac deaths from the ingestion of marine n-3 PUFAs, along with the recent availability in the UK of its pharmacological equivalent, Omacor™. Secondary prevention trials, such as the Diet and Reinfarction Trial (DART) and the more recent analysis of the GISSI-Prevenzione data, found a reduction in sudden deaths associated with supplementation of n-3 PUFAs in post-myocardial infarction patients.[1,2]

In the primary prevention of coronary heart disease, the US Physicians Health Study and the Nurses Health Study found that in patients with no known cardiovascular disease, a diet rich in fish oils reduced the risk of sudden cardiac death.[3,4]

Despite the convincing beneficial effects shown by these fish oils on cardiovascular disease, highlighted by Izzat and Avery in their comprehensive review in this issue of *The British Journal of Cardiology* (see pages 600-09), the actual mechanism through which they exert their cardioprotective effects is still not clear. This may involve several pleiotropic effects acting on different aspects of the cardiovascular system, including potential anti-atherosclerotic, antithrombotic, anti-arrhythmic, and myocardial effects.

Large-scale epidemiological studies, clinical intervention trials and – more recently – animal studies, appear to suggest the anti-arrhythmic mechanism of action of n-3 PUFAs is the most important, especially since the predominant beneficial effect from ingesting marine n-3 PUFAs was in preventing sudden cardiac death with no protection shown against non-fatal myocardial infarction.

Anti-arrhythmic action

The actual mechanism involved in their anti-arrhythmic action is not known but either inhibition of voltage-dependent sodium currents or inhibition of L-type calcium currents have been implicated. The hypothesis surrounding the role of the voltage-dependent sodium channel relates to the excitability of the cardiac tissue: with ischaemic tissue being partially depolarised, the voltage-dependent sodium channel is more likely to be activated by a small depolarising stimulus, which could then initiate an arrhythmia. In the presence of n-3 PUFAs, however, the membrane potential is hyperpolarised or 'stabilised' and therefore less likely to undergo a spontaneous depolarisation required for arrhythmia induction.[5] With reference to the effect of n-3 PUFAs and calcium currents, inhibition of the L-type calcium channel leads to a reduction in cytosolic calcium, thereby decreasing the arrhythmic potential of that cell.[6]

More recently it has been shown in an animal model that n-3 PUFAs may inhibit sarcolemmal Na^+/H^+ exchange.[7] This exchanger normally transports H^+ out of the cell in exchange for Na^+; this contributes to the rise in cytosolic Ca^{2+} during ischaemia-reperfusion. During ischaemia there is a rise in intracellular H^+ due to the accumulation of lactic acid. The

exchanger works to extrude H^+, resulting in the transport inwards of Na^+. This rise in intracellular Na^+ triggers the Na^+/Ca^+ exchanger to extrude Na^+, which results in Ca^{2+} entry into the cell, leading to Ca^{2+} overload and the generation of arrhythmia and cell death.

It is intriguing to speculate, therefore, that inhibiting Na^+/H^+ exchange may be a potential mechanism by which n-3 PUFAs protect the myocardium from arrhythmias and cell death. Indeed, one of the most potent ways of protecting the heart from ischaemia-reperfusion injury is by inhibition of Na^+/H^+ exchange.[8] Furthermore, clinical studies, using the Na^+/H^+ exchange inhibitor, cariporide, have shown significant benefit providing the drug was present prior to the index ischaemic event.[9] Whether n-3 PUFAs provide similar means of myocardial protection via their ability to inhibit Na^+/H^+ exchange remains unknown but an interesting possibility.

Summary

The overwhelming clinical evidence in support of the cardiovascular benefits of ingesting n-3 PUFAs should help direct us towards implementing recommendations made by the American Heart Association. These promote an intake of 1 g of n-3 PUFAs daily, which could be achieved either by diet or pharmacological supplements, such as Omacor™.

References

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