British Journal of Pharmacology (2007) 150, 258–260
 0007–1188/07 $30.00
www.brjpharmacol.org

COMMENTARY

ω-3 Polyunsaturated fatty acids (PUFAs or fish oils) and atrial fibrillation

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British Journal of Pharmacology (2007) **150,** 258–260. doi:10.1038/sj.bjp.0706978; published online 18 December 2006

In this issue of *Br J Pharmacol*, Da Cunha *et al*. (2007) describe the effect of the acute administration of fish oil (ω-3 polyunsaturated fatty acids) on the effective refractory period of canine atrium during a rapid pacing protocol for 6 h. Rapid pacing – for hours – causes a substantial decrease in action potential duration (Yue *et al*., 1997) and refractory periods (Wijffels *et al*., 1995) in the atrium, although, remarkably, not in the ventricle (Satoh and Zipes, 1996). The increase in knowledge from the present study (Da Cunha *et al*., 2007) is at first sight rather incremental. However, the finding that acute administration of these fish oils *completely* prevents the shortening of refractoriness in response to rapid pacing is very interesting. There are two confounding factors. First, there is no such thing as one type of atrial fibrillation. It is not known – and in fact highly improbable – whether changes induced by prolonged experimental rapid pacing are equal to changes that are caused by underlying factors in the clinical situation such as dilatation, increased pressure, changed neurohormones or ischaemia. The other confounding factor is that it is not known under what circumstances fish oils are beneficial. It is not known whether they exert their beneficial (or adverse…) effects by a direct ligand type of action or by incorporation into the sarcolemma. These two confounding factors are addressed in the next two paragraphs followed by a brief outline of previous studies on the effects of fish oils in conditions of atrial fibrillation.

Atrial fibrillation

The authors start their paper by acknowledging that one of the three electrophysiological hallmarks of chronic atrial fibrillation, loss of adaptation of refractoriness to heart rate, was described in patients by Attuel *et al*. (1982) as early as in 1982. The other two changes, decreased refractoriness and increased dispersion were also described in clinical studies (Le Heuzey *et al*., 1989) well before their experimental confirmation in animal studies. To date, it remains unclear which factors are pivotal for the occurrence of a first attack of atrial fibrillation and which are more relevant for the transition from paroxysmal atrial fibrillation into a chronic state. The clinical studies (Attuel *et al*., 1982, Le Heuzey *et al*., 1989) merely demonstrate that all (three) hallmarks are present in the chronic state. The significance of experimental animal studies lies primarily in a better understanding of the aetiology of the disease. The decrease of refractoriness as well as its increased dispersion can be observed both in patients with paroxysmal and chronic atrial fibrillation (Ramdat Misier *et al*., 1992) and, therefore, appears not to play a role in the transition from the paroxysmal to the chronic state. Whether or not a decrease in refractoriness is necessary for a first attack is not known. The study by Da Cunha *et al*. (2007) suggests that fish oils may be effective either in the prevention of a first attack, or, in the exacerbation of single attacks into prolonged episodes of atrial fibrillation.

Atrial fibrillation is an arrhythmia with a longstanding history (for an excellent editorial on the history of atrial fibrillation, see Nattel *et al*., 2002). Several types of remodelling in atrial fibrillation have been described: electrical remodelling, contractile remodelling and structural remodelling (Allessie *et al*., 2002). However, the relationship between these three types of remodelling, as well as their relevance for different pathophysiological states, remain elusive. Recently, it was shown that drug efficacy is dependent on the mechanism of atrial fibrillation (Li *et al*., 2000; Nattel, 2002). It is expected that the efficacy of fish oils may also depend on the underlying mechanism.

Fish oils

The interest in fish oils was originally raised by low rates of coronary heart disease among Greenland Inuits (Bang *et al*.,

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Received 2 October 2006; accepted 17 October 2006; published online 18 December 2006

1971) and has led to numerous studies (for review see McLennan and Abeywardena, 2005). Increased intake of fish oil has reduced sudden cardiac death in some trials, but not in others (for review see Hooper *et al*., 2006) and thus produced an ambiguous picture. We have recently touched on two very relevant issues concerning fish oils. One is the underlying disease, the other is the mode of application. First, there is evidence that fish oils may be anti-arrhythmic under circumstances that favour triggered activity, but pro-arrhythmic under circumstances that may facilitate reentrant arrhythmias (Coronel *et al*., 2007; Den Ruijter *et al*., 2007). By and large, this would imply that fish oils are anti-arrhythmic in patients with heart failure (including patients with a healed myocardial infarction), but pro-arrhythmic in patients with angina pectoris (acute regional ischaemia). If this scenario mirrors reality, the efficacy of fish oil in clinical trials with mixed patient populations would be expected to be void, which indeed is the case in a systematic review (Hooper *et al*., 2006). In clinical trials with less variation in the underlying pathophysiology, fish oil supplementation may be either pro- or anti-arrhythmic (Den Ruijter *et al*., 2007).

Second, the mode of application may be equally important. It goes without saying that it makes a big difference whether a myocyte, healthy or sick, 'sees' the fish oil for the very first time, or that fish oils are part of a diet and are thereby not only present in plasma, but also incorporated in the sarcolemma. Verkerk *et al*. (2006) recently reported in a feeding study that incorporation of fish oils into the sarcolemma of porcine ventricle shortened action potential duration in isolated myocytes. Moreover, one inward current ($I_{Ca,L}$) and the Na^+/Ca^{2+} exchanger were decreased, whereas two outward currents (I_{Ks} and I_{K1}) were increased. All these changes in currents complied with the observed action potential shortening. The fact that these incorporated fish oils influenced multiple currents suggests that they do not act as ligands, but that they may change channel activity indirectly, for example by interfering with membrane fluidity. It should also be noted that in these experiments, fish oils were not present in the bath solution and that the incorporation was irreversible even in the presence of albumin, at least for the duration of the experiments. In general, acute administration of fish oil to myocytes (in contrast with feeding experiments) leads to variable effects on action potential duration as a function of both concentration and species (see for review Den Ruijter *et al*., 2007). In the study of Da Cunha *et al*. (2007), only the effects of acute administration of fish oils were assessed and their findings would certainly have been corroborated if the same prevention of action potential shortening during rapid pacing had been demonstrated in dogs fed a fish oil diet. Very recent data show that this is not the case (Sahabe *et al*., 2006).

Atrial fibrillation and fish oils

In diverse populations of elderly adults, two studies report contrasting findings on fish oil and atrial fibrillation (Mozaffarian *et al*., 2004; Brouwer *et al*., 2006). In a 12-year follow-up study, Mozaffarian *et al*. (2004) found an inverse correlation between incidence of atrial fibrillation and intake of tuna or other broiled and baked fish, albeit not with the intake of fried fish or fish sandwiches. Brouwer *et al*. (2006) did not find an association between intake of fish oil and the onset of atrial fibrillation in a 6.5-year follow-up study. A drawback in the study of Mozaffarian is that it did not actually assess the intake of n-3 fatty acids other than by a questionnaire, whereas Brouwer *et al*. (2006) calculated n-3 fatty acid and fish intake. Another study also concluded that there was no association between fish oil and atrial fibrillation in healthy subjects (Frost and Vestegaard, 2005). The selected subjects in these studies were healthy at baseline and some of the participants in each study group developed atrial fibrillation during the study. The onset of atrial fibrillation may have numerous causes, among which previous myocardial infarction, or congestive heart failure (see above). Therefore, an initially healthy population of patients may divert into an inhomogeneous patient population with different mechanisms of atrial fibrillation, and this may explain the ambiguous results in these cohort studies. A randomized controlled trial investigated the efficacy of fish oil in preventing post-operative atrial fibrillation in patients undergoing coronary bypass graft surgery. Fish oil supplementation was started after randomization of the patients for at least 5 days until surgery and continued after surgery. Fish oil supplementation reduced the incidence of post-operative atrial fibrillation markedly from 33 to 15% and also resulted in a shorter stay in hospital (Calò *et al*., 2005). Thus, supplementation of fish oil for 1 week already affects atrial electrophysiology. It is uncertain whether supplementation of fish oil for 1 week is enough to ensure incorporation into the atrial sarcolemma. So, whether this reduction in atrial fibrillation is due to 'circulating' fish oils in the blood or to fish oil incorporation into the sarcolemma, or both, remains unclear.

The efficacy of dietary fish oil at preventing atrial fibrillation was tested in a rabbit model of stretch-induced atrial fibrillation (Ninio *et al*., 2005). A dietary supplement of fish oil for 12 weeks reduced the stretch-induced drop in refractory periods and reduced the stretch-induced susceptibility to atrial fibrillation. From both experimental studies (Ninio *et al*., 2005; Da Cunha *et al*., 2007), it can be concluded that fish oil prevents both stretch-induced and rapid pacing-induced electrical remodelling of the atrium and this may have important implications for atrial fibrillation.

Thoughts on arrhythmogenesis

The study of Da Cunha *et al*. (2007) is the first to demonstrate that acute administration of fish oil completely prevents electrophysiological remodelling in response to rapid pacing. It is to be expected that this may either prevent the onset or the perpetuation of atrial fibrillation. However, this could not be adequately tested in the present investigation for obvious reasons. If the animal model does not show arrhythmias in the control situation, it is impossible to demonstrate an anti-arrhythmic effect of the intervention. The same group of authors have previously demonstrated a

100% efficacy of fish oils in the prevention of ventricular fibrillation in dogs with acute regional ischaemia in combination with an old infarct, exercise and reperfusion (Billman *et al*., 1999). This animal model was at the other site of the spectrum. If an animal model, purely by design, has a 100% incidence of arrhythmias at baseline, it becomes impossible to demonstrate pro-arrhythmia.

In conclusion, the relationship between fish oil and the incidence of atrial fibrillation deserves more research. We feel that a more definitive answer may come from experimental animal studies with intermediate incidence of atrial fibrillation in one particular condition, for example, atrial dilatation, and from randomized controlled trials with patient groups in which mechanisms of atrial fibrillation are, at least in part, known.

Acknowledgements

This work was funded by the Netherlands Heart Foundation (grant 2003B079) and the SEAFOOD plus program of the European Union (grant 506359).

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