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news

Niaspan: new hope for heart patients

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Scientists have found an effective way of slowing the progression of heart disease – one of the leading causes of death in the western world. Researchers from the Walter Reed Army Medical Centre (http://www.wramc.amedd.army.mil/) in Washington have found that a combination of two drugs – one that increases 'good' cholesterol and one that lowers 'bad' cholesterol – can slow the progression of atherosclarosis more effectively that using one drug alone. This study, called ARBITER 2, is the first to test a two-pronged approach to treat cardiovascular disease (CHD) – using Niaspan (a form of nicotinic acid) to raise high density lipoprotein (HDL) and a statin to lower low density lipoprotein (LDL).

Targeting not just LDL but HDL too

The results were announced at the recent American Heart Association (http://www.americanheart.org) meeting in New Orleans and are available online in the journal *Circulation*. Commenting on the significance of the results, Allen Taylor, who led the study, said 'It leads us into a new era of combined therapy targeting not just LDL but HDL for reduction of CHD risk'.

The trial followed 149 patients, all of whom were being treated with statins for their coronary heart disease. One group of patients were given Niaspan in addition to a statin (most were on simvastatin) and the second group received a statin plus a placebo. After just one year, those who received the combined therapy had little or no progression of atherosclerosis and their HDL or 'good' cholesterol was raised.

Flushing

Statins, introduced in the 1990s, have been very effective in treating cardiovascular disease by lowering LDL, but have less of an effect on HDL, which helps remove cholesterol from the body. To raise HDL, physicians prescribe nicotinic acid. However, it has unpleasant side effects; patients experience 'flushing' a prickly hot sensation on the skin, which is caused by prostaglandin production, causing some to stop taking the drug. This new form of the drug, Niaspan – a prolonged-release nicotinic acid – produces a more continues effect and less frequent and less severe flushing in patients. 'Even with individuals that do flush, with Niaspan the flushing goes down to once per month', said John Chapman, from Hôpital de la Pieté, Paris.

Pointing out the advantages of Niaspan, Chapman added, 'Niaspan attenuates the ischemia seen in myocardial infarction… we are becoming aware of the additional therapeutic actions of nicotinic acid, all of which are beneficial'.

> **'One of the goals is an increase in awareness of the importance of good cholesterol, to identify individuals at risk'**

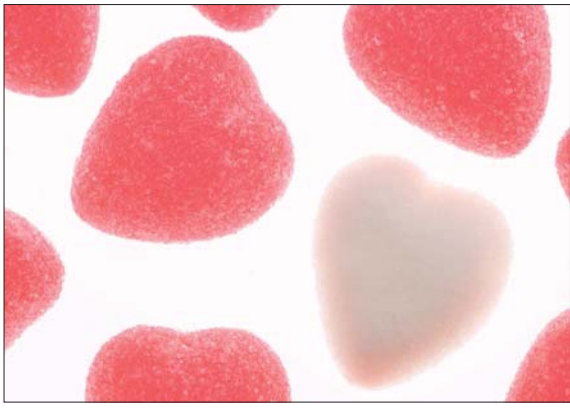
Raising awareness

Clinicians hope that this study will raise awareness of the importance of targeting HDL in cardiovascular disease. Although Taylor believes that HDL was not neglected in the past but rather 'it is just now the fertile ground that we are turning our attention to, as we realize the important protection afforded by statins is meaningful but incomplete'. 'One of the goals is an increase in awareness of the importance of good cholesterol, to identify individuals at risk' said Chapman, who looks forward to the day when physicians in the UK will measure both types of cholesterol (LDH and HDL) in those at risk – something that is routinely done in many other European countries.

Although nicotinic acid might be the most potent drug available to raise HDL, lifestyle changes can also help. 'Vigorous exercise, moderate alcohol intake and smoking cessation all work [to raise HDL]', said Allen. 'Drugs that can increase HDL include statins and fibrates (to a relatively small degree) and the new compound rimonabant', he added.

A polypill?

So will these dual therapies lead to the production of a 'polypill' – where a number of drugs are combined in a single pill?



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'Combination of niacin–lovastatin is already available in the USA and some statin–niacin combinations may become available in Europe in the future', said Anthony Wierzbicki from St Thomas' Hospital in London. 'Given compliance issues with multiple drugs… and the need for multiple medications in patients with CHD, combinations are the only way forward', he added. 'Polypills are on the horizon- but, my personal opinion is that the individual formulations must be tested, and the multiple dose combinations needed for flexibility make a polypill a complicated solution', concluded Taylor.

References

1 Taylor, A.J. (2004) Arterial Biology for the Investigation of the treatment effects of reducing cholesterol (ARBITER) 2. *Circulation*. DOI:10.1161/01.CIR.0000148955.19792.8D (Epub. ahead of print; www.circulationha.org)

Silence of the poppies: a new source of drug precursors

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Australian researchers have used RNA interference (RNAi) technology to metabolically engineer the opium poppy for the first time. Unexpectedly, by silencing one of the last enzymes in the biosynthetic pathway leading to codeine and morphine, the researchers produced a poppy that accumulates reticuline, a nonnarcotic alkaloid intermediate, well upstream of codeine [1]. 'Our research opens up the possibility of forcing the accumulation of potentially useful intermediates that do not normally accumulate to any extent in the poppy,' says Philip Larkin of CSIRO Plant Industry (Canberra, Australia; http://www.pi.csiro.au).

Designer poppies

Opium poppy is one of the oldest cultivated medicinal plants – the Sumerians grew *Papaver somniferum* in 6000 BC for its analgesic properties. Codeine and morphine, alkaloids that accumulate in the latex of the poppy, are two of the most important analgesics in use today. Other intermediates in the morphine biosynthetic pathway are also of medical importance, particularly as feedstuffs for drug synthesis. The intermediate thebaine, for example, is used to synthesize the analgesics buprenorphine and oxycodone.

'To achieve our long-term objectives of improving the yields of useful intermediates, we need to understand which genes in the pathway leading to codeine and morphine are limiting; we need to understand the control of secondary metabolism in the poppy,' explains Larkin, who collaborates with Tasmanian Alkaloids (http://www.tasalk.com.au), a major producer of the world's legally traded opiates.

Larkin and co-workers recently used RNAi to silence codeine reductase (COR), a multigene family of enzymes that convert codeinone and morphinone to codeine and morphine, respectively [1]. 'We designed a hairpin RNA construct to regions found in all the COR genes and, somewhat surprisingly, obtained poppies that accumulate reticuline, a compound that is formed seven enzyme steps before codeinone.' Reticuline, notes Larkin, is the starting point for the synthesis of bisbenzylisoquinoline alkaloids, some of which have shown promise as antimalarial and anticancer compounds. 'The existence of this transgenic poppy might encourage drug discoverers to follow up on interesting bioactivities that can be made from reticuline,' he suggests.

> 'The poppy is a fantastic platform for pharmaceutical production'

Understanding alkaloid biosynthesis

'We have seen similar results in California poppy,' comments plant biotechnologist Peter Facchini (Department of Biological Science, University of Calgary, Canada; http://www.bio.ucalgary.ca), 'in that by removing just one enzyme in the alkaloid synthesis pathway, we disrupted the whole pathway [2]. Larkin's well-done research provides important insights into a complex process about which we know relatively little but which we need to understand before we can engineer poppies to produce useful intermediates.'

Both Larkin and Facchini believe that poppies have a great future for drug discovery and development. 'The opium poppy is going to become the number one system for learning how plants make alkaloids,' says Facchini. 'What we learn in poppies might help us to understand how the periwinkle makes vinblastine, for example,' and ultimately lead to better sources for this and other plant-derived medicinal compounds. 'The poppy is a fantastic platform for pharmaceutical production,' agrees Larkin, 'but drug discovery teams and plant geneticists need to work together to exploit it fully. With good collaborations, we may be able to get the poppy to do some of the fancy chemistry necessary for the discovery and production of new drugs.'

References

1 Allen, R.S. *et al.* (2004) RNAi-mediated replacement of morphine with the nonnarcotic alkaloid reticuline in opium poppy. *Nat. Biotech.* DOI: 10.1038/nbt1033 (Epub. ahead of print; http://www.nature.com/nbt)
2 Park, S.U. *et al.* (2003) Modulation of the berberine bridge enzyme in transgenic root cultures of California poppy alters the accumulation of benzophenanthridine alkaloids. *Plant Mol. Biol.* 51, 153–164

1359-6446/04/$ – see front matter PII: S1359-6446(04)03335-5