news

From fat to fit

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Protection against cardiovascular (CV) disease, an increased ability to burn fat and enhanced athletic performance: if a drug could be developed to confer any one of these three properties, it would be a blessing to thousands. Scientists at the Salk Institute in La Jolla, CA, USA, are currently engaged in research that could lead to all three.

Syndrome X

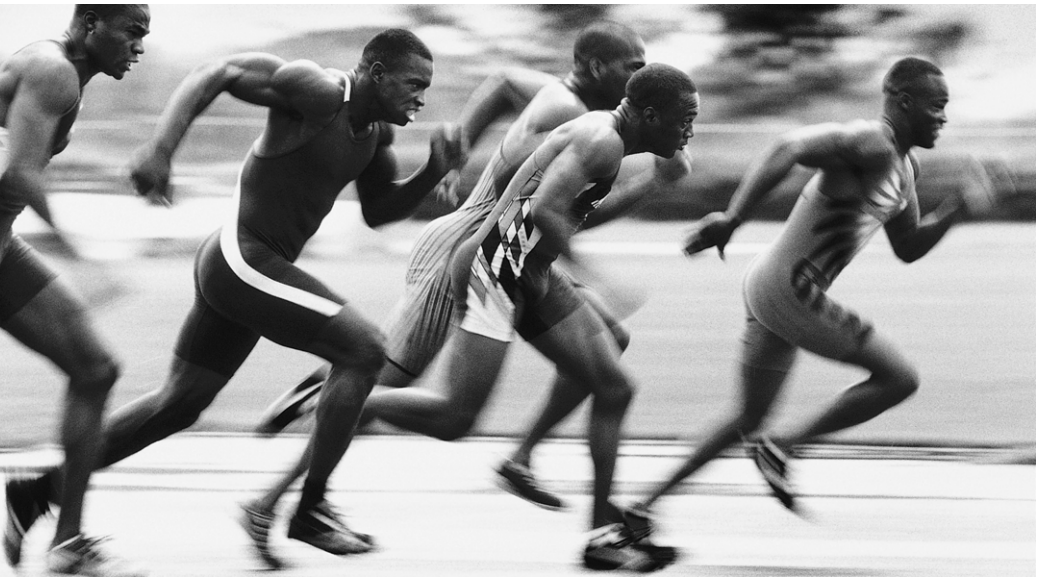
Lack of exercise, poor diet and obesity significantly contribute to the plague of the 21st century. Syndrome X is a collection of disease states arising from obesity, including resistance to insulin, diabetes and atherosclerosis. Rightly, healthcare professionals have tried for many years to tackle obesity at source, with diets – an approach focussing on appetite. Research by the Salk Institute group, led by Ronald Evans, could lead to Syndrome X and related conditions being tackled through a route unlinked to appetite or habit – the individual's metabolism (www.salk.edu/news/releases/details.php?id=123). 'Appetite is genetically determined', added Evans, 'people revert to their base appetite after a diet and regain the weight they'd lost'.

Evans' research centres on a receptor that is found in a number of tissues, but significantly in adipose, muscle and heart tissue. The peroxisome proliferator-activated receptor (PPAR) family is involved in the burning and storage of fatty acids. Of these, PPARδ is the least understood, but previous work by Evans' group had labelled this isoform as 'the obesity gene' because of its ability to regulate fat release and consumption in response to exercise and exposure to cold.

Twitching muscle types

The Evans group first looked at PPARδ in adipose tissue. Engineering an activating peptide into the amino acid sequence for the receptor, they found that the receptor could be permanently switched on. The effect of this activation on genetically altered mice was an increase in metabolic activity. Labelled fats were consumed by the mice, producing labelled water as a by-product, along with energy. Similar effects could be seen when the mice were given labelled triglycerides. Effectively, switching on PPARδ in adipose tissues led to increased fat burning.

Attention then moved to muscle tissue. Muscle tissue is where 80% of all the body's glucose is used or produced and that is why muscle tissue is so significant in obesity. When the body has excess calories, it burns fat and not glucose, leaving excess glucose. In turn, this leads to insulin resistance and ultimately diabetes. 'This is why exercise is especially good for diabetic or obese people', continued Evans. 'But most [obese] people don't exercise enough'. In muscle, PPARδ activation caused a change in the proportion of the two muscle fibre types – away from the fast-twitch type that burns glucose, in favour of the slow-twitch, fat burning type that is common in endurance athletes. Previously, such changes in fibre-type proportion had only been brought about through prolonged periods of exercise. The switch is best described by the effect it has on mice engineered to have PPARδ permanently switched on in their muscle tissue. Evans said, 'We created a "marathon mouse" that has an increased ability to run long distances'. Evans continued, 'Re-engineering muscle like this could help people who are very overweight and have trouble exercising. Medication could make exercising easier'.



Cardiovascular disease and PPARδ

CV disease is a third area where PPARδ activation could provide benefits. Active PPARδ suppresses inflammation in CV disease, potentially reducing the incidence or severity of atherosclerosis – the accumulation of lipids in the arteries.

In terms of how this research might develop into novel drugs, Evans is hopeful, but remains realistic. 'Molecules have been created [to activate PPARδ], and are under development within the pharmaceutical industry'. GlaxoSmithKline, for example, currently have a PPARδ agonist in Phase II trials (along with more generic PPAR ligands), and other companies are known to be developing PPARδ agonists, although not at such an advanced stage of development.

So, how might the future for PPARδ drugs look? Following recent doping scandals, could expectations be blighted by illicit use in sports? Evans agrees, 'There's no doubt of potential for drug abuse by athletes – in mice there's certainly a big advantage'. However, the positive side of PPARδ therapy is the direction in which research is moving – looking to develop drugs that are targeted to specific tissues. 'First generation drugs will be fairly non-specific', Evans believes. 'But we may find a similar scenario to the oestrogen receptor, where there are no tissue-specific subtypes of the receptor, but they exhibit tissue-specific behaviour'. It is certainly not difficult to see the money-making potential for PPARδ drugs. That alone should fuel their development, and ultimately some relief for patients suffering from obesity, diabetes or CV disease.

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