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Synopses of important papers published in specialty and other general medical journals

Orally active agents that mimic the effect of exercise

During aerobic endurance training such as running or swimming the myofibrils of skeletal muscle change their phenotype. This morphological change is accompanied by an increase in oxidative enzymes, glycogen and the numbers of glucose transporters (GLUT4). Importantly, these changes are accompanied by an increase in insulin sensitivity and an improvement in glucose homeostasis. Conversely, inactivity reverses these changes.[1]

A recent paper[2] confirms earlier findings that suggested that these changes involve gene expression regulated by a pathway linked to the peroxisome-proliferator-activated receptor delta (PPAR-δ) and AMP (3',5'-5-% adenosine monophosphate)-activated protein kinase. Using a PPAR-δ, agonist (GW501516) they show that in sedentary mice, in the absence of exercise, the administration of an oral compound can increase the expression of oxidative genes in muscle; the endurance of the mice was unaltered. However, in mice concurrently exercising on a treadmill there was a 70% increase in endurance compared with the exercising control group. Even more surprising was the finding that treatment of sedentary mice with an activator of AMP-activated protein kinase, AICAR (5-aminoimidazole-4-carboxamide-1-4-ribofuranoside), led to an improvement in exercise endurance of 44% over the sedentary controls. In just five days AICAR treatment increased muscle glycogen, GLUT4 and a number of mitochondrial enzymes. These results complement earlier results that showed AICAR to lower blood glucose levels and decrease obesity.

These quirky results highlight a great deal of research that suggests that therapeutic manipulation of this pathway delivers better drugs to combat metabolic diseases. Those who dread the adverse effects of even moderate exercise can take comfort from the possibility that red wine rich in resveratrol also activates an AMP-activated protein kinase.[3]

References

1 Goodyear LJ. The exercise pill – too good to be true? *N Engl J Med* 2008; 359(17):1842–4.
2 Narkar VA, Downes M, Yu RT et al. AMPK and PPAR delta agonists are exercise mimetics. *Cell* 2008;134(3):405–15.
3 Hwang JT, Kwon DY, Park OJ et al. Resveratrol protects ROS-induced cell death by activating AMPK in H9c2 cardiac muscle cells. *Genes Nutr* 2008; 2(4):323–6.

Subcutaneous exenatide once a week for diabetics

Exenatide was the first incretin mimetic approved in both the US and the EU for the treatment of type 2 diabetes and has been shown to increase glucose-dependent insulin secretion, reduce food intake and slow gastric emptying. In conjunction with one or more oral therapies, twice-daily injections have been shown to cause sustained reductions in haemoglobin 1c (HbA1c). Now in a new randomised, open-label, non-inferiority trial Drucker and colleagues have shown exenatide given as a subcutaneous injection once a week to produce greater glycaemic control than the twice-a-day regime. In addition, once-a-week injections appear to be associated with fewer side effects, in particular post-injection nausea. Importantly, there were no reports of major hypoglycaemic events on either treatment. Although at present NICE has recommended the restriction of twice-daily exenatide to patients with a high body mass index and those requiring a high dose of insulin, the development of a once-weekly formulation that results in a significant improvement in HbA1c in association with weight loss will make the use of prolonged GLP-1 receptor activation an even more attractive option.

Drucker DJ, Buse JB, Taylor K et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008; 372:1240–50.

John S Kelly

Underlying cancer in venous thromboembolism

This systematic review of underlying cancer in venous thromboembolism (VTE) selected 34 from 939 publications (9,516 patients) and is the largest available. The overall incidence of previously undiagnosed cancer at presentation with VTE was 4.1% and, within a year of follow-up, 6.3%. Most striking was the difference between cancers in VTE without an obvious cause (6.1% at presentation and 10% by a year) and VTE with a cause (1.9% and 2.6%). Limited investigation (clinical examination, routine blood tests, chest X-ray) at presentation detected 47.6% of cancers, increasing to 69.7% with abdominal and pelvic imaging and tumour markers (PSA, CEA, cancer antigen-125). A total of 123 early cancers were found, 17 by limited investigation and 27 by additional investigations. Cancer is common in VTE without an obvious cause; two-thirds can be diagnosed on investigation, including some early cancers, but the impact of this on morbidity and survival is unknown.

Carrier M, Le Gal G, Wells PS et al. Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? *Ann Intern Med* 2008;149(5):323–33.

Niall Finlayson

Middle-ear disease and schizophrenia

While the link between deafness and paranoid disorders has been heavily researched, only one study had examined the possibility that middle-ear disease per se might be linked to schizophrenia – and it found an association. A case-control study (n=84; four controls per case), with improved methodology, has replicated this. Patients were assessed audiologically and by psychiatric interview, although the independent variable remained presence or absence of middle-ear disease documented in the primary care records. Middle-ear disease recorded prior to the emergence of schizophrenia was over-represented, odds ratio = 3.96 (95% CI 1.86–7.28), so it may be aetiologically important in the development of some cases of schizophrenia.

Mason P, Rimmer M, Richman A et al. Middle-ear disease and schizophrenia: case-control study. *Br J Psychiatry* 2008; 193:192–6.

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