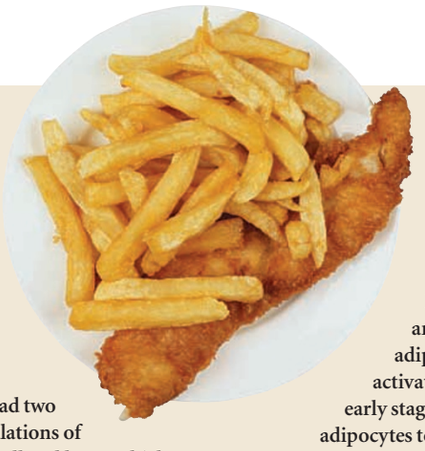
OBESITY

Adipocyte metabolism



Obesity is an increasing problem, with more than one billion people worldwide classed as overweight and at high risk for developing other serious conditions, such as heart disease and diabetes. Obesity is closely associated with metabolic syndromes, and is typically characterized by insulin resistance in muscle, liver and fat, and by defects in insulin secretion from pancreatic β-cells. It has become clear that adipocytes are important in this process. Two reports published in *Developmental Cell* provide exciting new perspectives about regulation of adipocytes and their role in disease pathogenesis.

In the first study, Kahn and colleagues bred mice that lacked the insulin receptor in their fat cells. These animals are called fat-specific insulin-receptor knockout (FIRKO) mice. This work exploited the Cre–*lox* technology for tissue-specific disruption of protein expression, which is a powerful approach to analyse complicated and interacting biochemical pathways. FIRKO mice had a lean body mass and differed from control mice in that they were protected from obesity associated with age or overeating. Importantly, they were also protected from developing obesity-associated or age-related insulin resistance, which leads to diabetes. Interestingly, FIRKO mice had two different populations of adipocytes, small and large, which differ in expression of the enzyme fatty-acid synthase and the transcription factors C/EBPα (CCAAT/enhancer binding protein-α) and SREBP1 (sterol-regulatory-element-binding transcription factor 1). It is thought that loss of the adipocyte insulin receptor unmasks differences between two sizes of fat cell, and that the small adipocytes are somehow protected against excessive fat loading, preventing the mice from becoming obese. Although FIRKO mice show insulin resistance in the adipose tissue, whole-body glucose metabolism is not affected.

In a second study, Auwerx and colleagues looked at the role of E2F cell-cycle regulators in the maturation of pre-adipocytes into adipocytes. E2Fs regulate cell proliferation, and there is evidence that they participate in adipocyte maturation. Using transgenic and chimeric mice, the authors show that E2Fs directly regulate the production of peroxisome proliferator-activated receptor-γ (PPAR-γ), a protein that is known to be crucial in the control of terminal adipocyte differentiation. Two E2F family members, E2F1 and E2F4, are involved in the process, and have opposing effects on adipocyte maturation. E2F1 activates PPAR-γ production at an early stage of development, allowing pre-adipocytes to proliferate, whereas E2F4 represses PPAR-γ during a later stage, when pre-adipocytes differentiate into mature adipocytes. The absence of E2F1 impairs adipogenesis, making this molecule a potential therapeutic target for obesity.

Insulin and insulin-like growth factors drive cell proliferation, including the proliferation of pre-adipocytes. Furthermore, insulin signalling in mature adipocytes is crucial for the development of obesity. Together, these papers have begun to unravel the complex control of adipocyte proliferation and insulin signalling in these cells, and how this process leads to obesity and other metabolic syndromes.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPERS Bluher, M. *et al.* Adipose tissue selective insulin receptor knockout protects against obesity-related glucose intolerance. *Dev. Cell* **3**, 863–876 (2002) | Fajas, L. *et al.* E2Fs regulate adipocyte differentiation. *Dev. Cell* **3**, 877–887 (2002)

ANTIPSYCHOTICS

How Goldilocks is partial to dopamine receptors

Aripiprazole is the first of the next-generation atypical antipsychotic drugs. It has been called a 'Goldilocks-like' drug, as it is a partial agonist — meaning it shows not too much agonist and not too much antagonist properties — in contrast to the existing dopamine antagonist treatments. Aripiprazole has been shown in some studies to be as effective as current antipsychotics, such as haloperidol, and have fewer side effects, but how the partial agonism could explain the range of activities of the drug was not fully known.

To clarify this, Milinoff and colleagues looked at the interactions of the drug with the recombinant human dopamine D_2 receptor, D2L. Their studies, published in the *Journal of Pharmacology and Experimental Therapeutics*, report that aripiprazole showed characteristics of a partial agonist in binding-affinity and cyclic-AMP-accumulation studies. Also, partial receptor inactivation reduced the maximum effect of aripiprazole on inhibition of cAMP accumulation at concentrations that did not alter the effect of the agonist dopamine, and increasing concentrations of aripiprazole blocked the action of dopamine equal to the agonist effect of aripiprazole alone. Finally, the efficacy of aripiprazole differed to that of dopamine, depending on the density of D2L receptors; and modulating the density of receptors affected the action of aripiprazole — aripiprazole behaved like an agonist in the presence of a receptor reserve for dopamine, but in its absence behaved like an antagonist.

So, the authors conclude that this, and previous studies (showing the partial agonism of 5-hydroxytryptamine $(5\text{-HT})_{1A}$ serotonin receptors and antagonism of 5-HT_{2A} serotonin receptors), support the model that aripiprazole belongs to a class of treatments known as dopamine–serotonin system stabilizers (DSSs). This partial-agonist activity of aripiprazole at D_2 receptors, the authors say, could explain the observed unique activity and the sustained efficacy of the drug.

Simon Frantz

References and links

ORIGINAL RESEARCH PAPER

Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. Burris, K. D. *J. Pharmacol. Exp. Ther.* **302**, 381–389 (2002)