

# Neuro-endocrinology

## BRIEFINGS

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### SUMMARY

Cannabis exerts its actions by mimicking 'endocannabinoid' neuromodulators at CB1 receptors in brain and peripheral tissues. The endocannabinoids both stimulate appetite by increasing food craving and enjoyment and promote the deposition of energy as fat in adipose tissues. These findings have raised the possibility of CB1 antagonists as a novel class of anti-obesity agents.

*Pseudocolour images of the density of CB1 receptors in rat brain at the level of the nucleus accumbens (NAcc). Compared to a lean animal fed a standard laboratory diet (top), the brain of a rat that became obese through overconsumption of a highly palatable 'cafeteria' diet (bottom) shows reduced CB1 density in the NAcc. This change is indicative of down-regulation of CB1 receptors through increased endocannabinoid release in response to the diet's sensory properties, to overconsumption, or to the development of obesity.*

Courtesy of Jo Harrold, University of Liverpool.

## ENDOCANNABINOIDS AND THE NEUROCHEMISTRY OF GLUTTONY

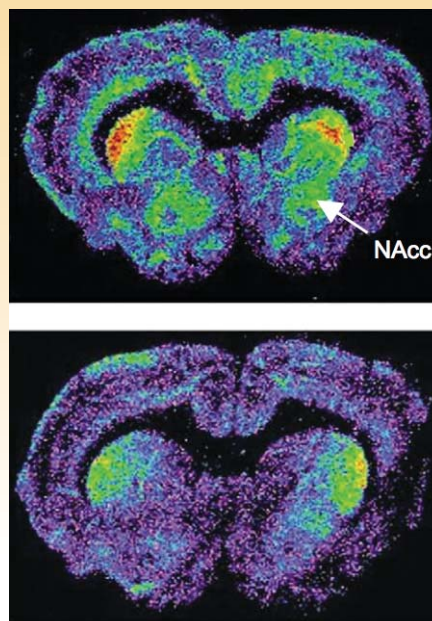
### The power of food

It is usual in the biological sciences to consider food intake as part of a homeostatic system balancing energy input and expenditure to maintain stable body weight. While homeostatic models are useful, and patently demonstrable in other areas of physiology (such as the fine control of water and electrolyte balance, and the regulation of thirst or sodium appetite), our appetite for food is undeniably subject to powerful external, psychologically-mediated influences. Most of us are only too aware of the power of food to stimulate appetite even when we are replete: think of the temptation to eat on the sight of delectable foods in a shop display, the urge to overconsume when faced with the variety of

a buffet, or our ability to override even physical discomfort to cram in that special dessert. Gluttony is part of our evolutionary heritage and, far from maintaining a precise balance between energy input and expenditure, we have motivational mechanisms that strive to maximise nutrient intake and highly efficient systems for the apparently unlimited storage of excess energy. Our susceptibility to the potent sensory – even imagined – properties of foods is one of the principal causes of obesity: the consequence of psychological systems that respond to food palatability and variety operating in a world of abundant appetising, cheap and all too energy-dense foods.

### Models of greed and hedonism

Biopsychological approaches to these issues emphasize motivational factors, particularly the craving for, and enjoyment of food. It's currently considered that appetite is subserved by two separable – albeit interactive – neural systems in the brain that respectively mediate food 'wanting' and 'liking'. The mesolimbic dopamine pathway, emanating in the ventral tegmental area and terminating in the nucleus accumbens, is key to 'wanting' and is critical to the assessment of incentive value or motivational salience of food: it orients us to food-related stimuli



when we are hungry, promotes our interest in novel or unexpected sources of nutrients, and is essential to food craving. In contrast, neural circuits within the nucleus accumbens are key to the hedonic evaluation of foods as we eat, influencing meal size and encouraging overconsumption of palatable food. Pharmacological manipulation of neural activity in these separate systems can critically influence the extent to which we want or like food, and so determine whether we eat, and how much.

### Cannabinoids in wanting and liking

The psychological actions of *Cannabis sativa* (marijuana) result from the agonist actions of the cannabinoid  $\Delta^9$ -tetrahydrocannabinol (THC) at specific cannabinoid CB1 receptors expressed in different brain regions, including the ‘wanting’ and ‘liking’ systems centred on the nucleus accumbens. The ‘munchies’ of cannabis folklore thus comes from the ability of THC to mimic the actions of the natural agonists for these receptors, the ‘endocannabinoids’. Thousands of years of human experience with cannabis have helped guide research exploring the biological role of these neuromodulators in normal appetite controls.

Administration into the brain (and particularly the nucleus accumbens) of the endocannabinoids *anandamide*, *2-arachidonoylglycerol* (2-AG) or *noladin ether* stimulates eating in laboratory animals, while blockade of CB1 receptors by antagonists, such as rimonabant, reduces food intake. Importantly, behavioural studies show that cannabinoids primarily accentuate food’s incentive value: even fully-satiated rats will quickly approach food and resume eating far

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*“...obesity has been linked to increased cannabinoid activity in both brain and periphery”*

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earlier than untreated animals, and animals will also work much harder than normal to obtain food after CB1 agonist treatment. Fasting, which naturally increases food craving, is also associated with increased brain anandamide and 2-AG levels, which in turn potentiate the activity of the mesolimbic ‘wanting’ circuits.

Endocannabinoids also appear to modulate the hedonic ‘liking’ aspects of eating: enhanced enjoyment of food after CB1 stimulation is implicit in the anecdotal accounts of cannabis users. Laboratory animals cannot give us subjective reports, but behavioural paradigms that can adequately assess hedonic evaluation in rats and mice reveal that anandamide, 2-AG and THC all produce changes in ingestive behaviour that are compatible with enhanced food palatability (CB1 antagonists have opposite effects). Notably, anandamide increases ‘liking’ when directly administered into the specific areas of the nucleus accumbens that mediate these positive hedonic responses.

### A target for pharmacotherapy

Endocannabinoids have also been linked to peripheral metabolic processes involved in storing excess energy in adipose tissue. For example, liver and fat cells express CB1 receptors and their stimulation leads to increased lipogenesis and fat deposition. As well as reducing food intake, CB1 antagonists can reverse these actions, and possibly also

increase energy utilization. Endocannabinoids, acting to promote both energy intake and storage, are therefore very likely to be crucial to the development of obesity. In fact, obesity has been linked to increased cannabinoid activity in both brain and periphery.

The combined actions of CB1 antagonists on central and peripheral systems naturally led to their promotion as anti-obesity agents, with rimonabant being the first of its class to be prescribed for weight loss and normalisation of the obesity-related ‘metabolic syndrome’. So far, the utility of these drugs has been hampered by side effects that reflect the normal involvement of endocannabinoids in multiple psychological and physiological processes. However, the endocannabinoid system – with its dual motivational and metabolic components – still represents a fascinating therapeutic target for the treatment of disorders of appetite or body weight, and their associated diseases.

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