

Blundell J E. Is there a role for serotonin (5-hydroxytryptamine) in feeding?

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Experimentally induced changes in the activity of serotonin neurons are associated with pronounced changes in feeding behaviour. In general, treatments and procedures believed to lead to an increased availability of 5-hydroxytryptamine (5-HT) in the synaptic cleft or that directly activate 5-HT postsynaptic receptors reduce food consumption, while procedures that either directly or indirectly decrease 5-HT receptor activation bring about the opposite effect. [The SCI[®] and SSCI[®] indicate that this paper has been cited in over 150 publications, making it this journal's most-cited paper.]

Neuropharmacology, Hunger, Satiety, and Anorexia

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The ideas behind this article were generated during research on the neuropharmacology of hunger motivation with Jac Herberg at the Institute of Neurology in London during the late 1960s. At one stage I was seeking a compound that could be used as an active control for amphetamine in pharmacological studies on anorexia for both central and peripheral administration; that is, a drug that gave rise to anorexia but lacked the motoric stimulation of amphetamine. Halogen-substituted phenylethylamines seemed promising, and the best of these was (\pm) fenfluramine. Most research on this drug had been done by Jacques Duhault in Paris and Silvio Garattini's group in Milan, and there was every indication that the anorexic property was dependent upon its serotonergic activity.¹ Looking around, it became clear that data on the relationship between food intake and 5-hydroxytryptamine (5-HT) existed in many locations and included work on precursors of 5-HT, releasers, re-uptake blockers, receptor agonists and antagonists, and brain indole changes following lesions, knife cuts, and neurotoxin administration.

During this period the neural control of appetite was a central issue in the study of the physiology of motivation. Why had this body of data apparently gone unnoticed? I believe the major reason is that the *Zeitgeist* of the period favoured an interpretation of neurochemistry and feeding relationships via catecholamine transmitters. However, today it is widely recognized that serotonin is one of the principle neurotransmitters operating as a link in the satiety cascade. The accumulated evidence indicates that serotonergic manipulations bring about a biologically understandable organization of the pattern of feeding behaviour.² There is now some evidence that the 5-HT component in the chain of neurochemical events underlying the expression of appetite is linked to the action of cholecystokinin—the prime peripherally acting agent mediating satiation.³

Why has this article been cited so frequently? One reason is that it provided the first clear and unequivocal statement of the relationship between serotonin, satiation, and hunger motivation. However, the statement was also substantially accurate and anticipated later developments. One important aspect of serotonin and appetite is that this transmitter intervenes in interrelationships among nutrition, neurochemistry, and behaviour such as those postulated by John Fernstrom (Pittsburgh), Dick Wurtman (MIT), and Harvey Anderson (Toronto). There is a long way to go before the complexities of this issue are worked out;⁴ but investigations focusing on serotonin have already acted as a catalyst for work on the relationships between nutrition, mental states, and actions.

Another development that has elaborated the role of serotonin in appetite control is the description of a number of receptor subtypes. Significantly, drugs that act as 5-HT_{1A} agonists, such as 8-OH DPAT, augment food intake.⁵ This effect is in keeping with the postulated existence of 1A type autoreceptors on the cell bodies of the raphe nuclei. This argument keeps intact the major principle of the original hypothesis, namely, that intensifying postsynaptic receptor activity will lead to hypophagia. However, the situation is clearly more complex than this since it appears that activation of at least three types of 5-HT receptor (1_A, 1_C, and 2) constitutes a sufficient condition for the suppression of food consumption.

The biological relevance of these effects has yet to be demonstrated, and it will take a while for a truly coherent picture to emerge from this mass of data. One important consideration is the establishment of criteria for sufficient and necessary conditions linked to anorexic action. Meanwhile serotonin manipulations produce clear adjustment of appetite in humans,⁶ an action with obvious therapeutic implications in the treatment of eating and weight disorders.

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