

Gut feelings

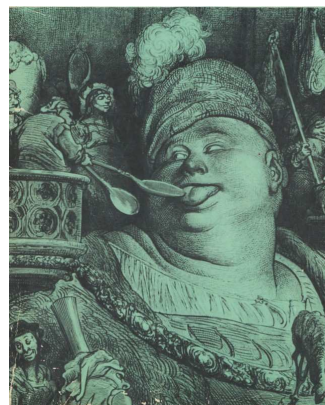
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The sensation of hunger would seem trivial to most, and yet – besides being vital – it implies complex molecular pathways both in our guts and our brain, as too does the perception of food sufficiency. Most of the time we are unaware, but we own a built-in system which tells us when our bodies could do with a little fuel, and when they can do without. An empty stomach – like a full one – does not go unnoticed. What is it that makes us feel hungry? Or full? Research on gut sensations has been blooming for years now, what with obesity spreading worldwide, and the molecular processes underlying appetite, or satiety, are slowly emerging. Ghrelin and obestatin are just two proteins which are an integral part of such processes, and are particular in that not only are they coded by the same gene but they have opposing actions. Indeed, ghrelin triggers off the desire for food, while obestatin reports adequacy.

Energy saving and spending should be part of a harmonious balance in any organism. However, besides a human propensity for gluttony or less frequently anorexia, the society many of us live in – which involves lack of exercise coupled with too much food – participates in tipping the balance. Overweight and obesity are common in many parts of the world. The condition was also known – though to a lesser degree – in Antiquity when, like today, it was not seen as a disease but more as something distasteful and the consequence of extravagant eating habits. One of the first descriptions of obesity and the idea of a possible surgical intervention on ‘alien flesh’ was given by the Roman author and teacher of rhetoric Claudius Aelian (170-235 AD), in his collection of historical miscellany ‘*Varia Historia*’ where he reported the most curious tales about well-known and less well-known figures of his time, or before. One of his stories recounts the case of a hugely obese statesman, Dionysius of Heraclea in Pontus, who lived during the 4th century BC and had a solid structure built around him to hide his plump parts, and from which only his head protruded.

Ghrelin, which participates in appetite stimulation, was discovered shortly before the turn of the century. Most of it is found in the stomach and the blood, although some is also present in tissues such as the kidney, the lungs, the immune cells and the hypothalamus...reflecting the fact that it could

well be involved in sensations other than just hunger. Researchers had noticed that the gene which coded for ghrelin could theoretically also code for another biologically active peptide. But it took a further five years to actually characterise it: obestatin.



‘Gargantua’, Gustave Doré

as depicted in ‘Five Books of the Lives, Heroic Deeds and Sayings of Gargantua and Pantagruel’ Francois Rabelais (1494-1553)

Obestatin, like ghrelin, is found in the stomach, the blood and the hypothalamus but, unlike ghrelin, obestatin informs us of satiety. Though both peptides may have a role *in situ*, they are probably part of an endocrine signalling

mechanism since both bind to two specific receptors which not only line the stomach but are also present in the hypothalamus. So, besides the surprising fact that the two peptides are two hormones with opposing actions – yet coded from the same gene – they also bear witness to a dialogue between our guts and our brain.

How do ghrelin and obestatin tell us that we are in need of energy or not? How either sensation is triggered off is unknown. However, during fasting periods, the amount of ghrelin increases in both our stomach and blood and, as we eat, its bulk fades away. The amount of obestatin, however, shows no particular variation. Both active peptides are small. Ghrelin – from the Indo-European root meaning ‘to grow’ – undergoes a unique posttranslational modification, octanoylation, without which the peptide cannot function. Obestatin – from ‘*obedere*’ meaning to devour in Latin – is posttranslationally amidated; a very common modification and essential to obestatin’s proper function.

Besides their binding to specific receptors, acting as hormones and being part of the appetite/satiety and gut/brain axis, both peptides have very different physiological consequences. Ghrelin stimulates appetite once its plasma level has reached a certain peak. It has direct effects

on digestive processes such as gastric acid secretion, the acceleration of gastric emptying, gastric motor activity and perhaps even gastroprotection. And if it contributes to obesity, it is because prolonged plasma ghrelin favours the stocking of fats. Although patients suffering from chronic obesity have little ghrelin in their plasma... Obestatin, on the other hand, checks gastric emptying as well as intestinal contractility. Which is exactly the opposite of what ghrelin does... As to the biological explanation of the actual sensations of *feeling* hungry, or *feeling* full with which we are so acquainted, that is a secret which is still selfishly kept by the hypothalamus.

Appetite suppressants have been widely in use since the 1950s. But the same problem always arises: side effects. Ghrelin and obestatin may provide different ways of interfering with appetite. Drugs could be designed according to the posttranslation modifications of the peptides, or to their receptors. Both have been injected into rats where, as hoped, ghrelin increased body weight, and obestatin suppressed body weight gain. We are not rats though. And in the case of obestatin, no one can deny that the rodents may just have felt nauseous and not wanted anything to eat... And, as always, no protein acts on its own. Ghrelin and obestatin are part of a huge process; touch one brick and the wall may come tumbling down.

Cross-references to Swiss-Prot

Appetite regulating hormones ghrelin and obestatin, *Homo sapiens* (Human) : Q9UBU3
Appetite regulating hormones ghrelin and obestatin, *Rattus norvegicus* (Rat) : Q9QYH7

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