

GHRELIN: A NEWLY DISCOVERED HORMONE

SUMMARY

Ghrelin is a gastric peptide that stimulates growth hormone secretion and increases adiposity. It is the first identified natural ligand for a previously cloned growth hormone secretagogue receptor which is present in the pituitary gland and the hypothalamic region of the brain. Insights into its regulation will now enable its physiological role to be elucidated and its potential clinical use evaluated.

Dual X-ray absorptiometry scan showing that body fat (white areas) is increased in mice treated with the growth hormone secretagogue (GHS), ipamorelin.

Modified from Lall, S. et al.,
Biochem Biophys Res Com **280**, 132-138, 2001.

Ghrelins and gremlins

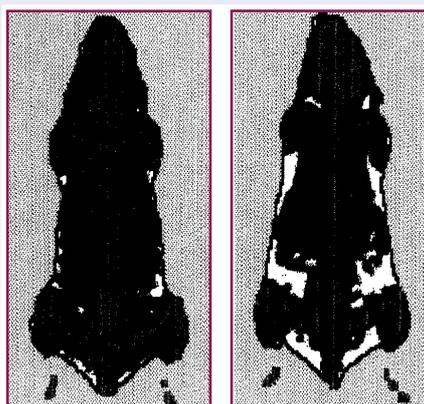
Aren't mobile phones marvellous? There I was in Stockholm on the day of the Nobel Prize Ceremony in December 1999, sitting on a bus when I received a memorable call. It was a moment anticipated for years with much speculation. Not my fantasy Nobel Prize (!) but a colleague informing me that a Japanese group had identified a natural ligand for the growth hormone secretagogue (GHS) – 'secretion-activating' – receptor. Its name was 'ghrelin'. Strange name, I thought, rather like 'gremlins', those ugly creatures with green skin, pointed ears and mischievous smiles that destroy aeroengines. 'Ghre' comes from an indo-european root for the word 'grow', a name thus not altogether surprising as ghrelin stimulates growth hormone (GH) secretion.

Ghrelin may have only been discovered a couple of years ago but its mechanism of action has been studied for around 25 years; particularly as it is potentially a magic potion to make children of short stature grow and to reduce muscle wastage in old age. In the late 1970s C.Y. Bowers placed the cart firmly before the horse when he provided the first synthetic GHS long before either a receptor or a natural GHS ligand had been identified. The first peptide GHS had weak GH-releasing activity but soon he found more potent substances.

Importantly, some GHS were orally active, opening up the possibility to obtain beneficial GH effects without GH injection (e.g. increased muscle mass, reduced body fat). Subsequently Roy Smith and colleagues successfully cloned a specific GHS receptor.

Ghrelin: a supernatural hormone

The big surprise revealed by the group that discovered ghrelin was its site of production. We had been speculating about this for years. Where might a natural GHS hormone be produced? Under what physiological conditions is it released? Perhaps release occurs when we need extra GH (e.g. when we exercise)? Is it produced by



Control

GHS treated

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Ghrelin: a newly discovered hormone

“Ghrelin turned out to be a gut peptide produced by the oxyntic glands of the stomach”

muscle? Is it a brain peptide interacting directly with the neuroendocrine circuits controlling GH secretion? If so, is it released into the blood supply to the pituitary? No! Ghrelin turned out to be a gut peptide produced by the oxyntic glands of the stomach. Since its discovery, sightings of ghrelin gene expression have also occurred in the placenta, kidney and hypothalamic region of the brain.

Potentially ghrelin is a newly discovered hormone but what is its physiological role? Ghrelin and GHS stimulate GH secretion by a direct pituitary action and also by activating hypothalamic systems that control GH secretion including, notably, the GH-releasing hormone (GHRH) neurones. Interestingly we found that GHS also activate hypothalamic circuits that have an established role in the control of appetite.

The Emperor's new clothes

Another giant leap in GHS/ghrelin research was the recent discovery that these compounds induce fat storage (i.e. adiposity). For many years, researchers had been treating rodents and humans with GHS looking for beneficial GH-dependent effects such as the well-known anti-obesity effect seen after GH injection. In two papers published around the same time, we and researchers at Eli Lilly reported that mice get fat following chronic GHS and ghrelin treatment. Perhaps, just

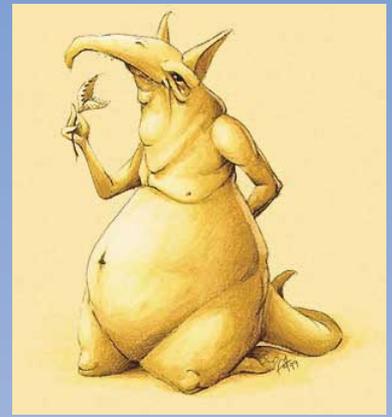
as in the Hans Christian Anderson fairytale, we didn't notice that the Emperor's nudity (or in this case, that the mice were getting fat) because we didn't want to believe it. GHS and ghrelin stimulate GH release and so we expected chronic treatment to reduce body fat rather than to increase it.

The mechanism by which ghrelin and GHS increase adiposity is not entirely clear. Acute treatment with these compounds rapidly stimulates feeding behaviour in rodents but we and others have not observed any overall increase in longterm food intake. Alternatively, increased adiposity could result from GHS/ghrelin effects to decrease energy expenditure and/or alter the body's preferences for fuel sources (i.e. carbohydrate rather than fat).

“Mice get fat following chronic GHS and ghrelin treatment”

Ghrelin's spell

Little is known about the role of ghrelin in the body or the physiological circumstances controlling its release from the stomach. Plasma levels of ghrelin are increased in fasted subjects which is rather unexpected for a hormone that also stimulates gastric motility and gastric acid secretion, both of which normally occur in response to food intake, in preparation for digestion. Also, the hypothalamus is more responsive to GHS/ghrelin during fasting; thus although endogenous ghrelin levels are high, the hypothalamic response to exogenous ghrelin is potentiated rather than suppressed. It has been suggested that ghrelin may act as a counter-



regulatory hormone to leptin, the adipose-derived hormone that suppresses hypothalamic feeding centres. Certainly, we have found that leptin suppresses the hypothalamic response to GHS.

Is gastric ghrelin a true hormone, released into the blood in sufficient concentrations to reach the neuroendocrine hypothalamus? If so, why might there be a need for a signal from stomach to hypothalamus that increases GH secretion and also increases adiposity? As is the case for many other gut hormones, it may be that gut-derived ghrelin is only active locally and does not influence the hypothalamus directly. We look forward to learning more about this mischievous hormone that has a special talent for causing mystery and destroying preconceived theories.

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