Editorial Focus: Hunger and satiety: one brain for two?

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running title: Amylin, CCK, BB, and the orexigenic effect of ghrelin
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Understanding the physiological controls of eating and developing effective pharmacological tools to reduce eating has never been more important. The modern world faces an unprecedented obesity epidemic, and the current treatment strategies are rather unsuccessful. One possible solution may be a combination or cocktail therapy. Obesity control research has been more focused on “long-term”, adiposity signals rather than the control of individual meals, which has been assumed to be rather plastic (34). Moreover, meal size appears to be under a confusingly large number of controls (27,30,33,34). One potential reason for this is that avoiding excessive meal size may be very important physiologically because large meals are major physiological stresses (32) that, at some point, may be unadaptive. This suggests that the controls of meal size, including many controls of the gut-brain axis, may indeed be very potent and are likely to open efficacious therapeutic opportunities. A related reason not to underemphasize the potential of meal controls in obesity therapy is the increasing evidence that the weight regulatory system based on leptin, insulin and other adiposity signals in fact seems more designed to stimulate eating and conserve energy when adiposity levels are too low rather than to inhibit eating and expend energy when adiposity increases (26).

The consequences of the multifactorial and redundant controls of eating in animals and humans for potential pharmacotherapy are ambiguous. It may be that manipulations of individual signals will be ineffective because of functionally antagonistic, adaptive responses by other signals. However, the wealth of signals also creates the potential for therapies based on simultaneous manipulation of several signals.
If many control signals operate simultaneously to control a single behavior, they must interact.

This addresses an important point: is food intake truly a single behavior? Total food intake being composed of many individual meals is regulated by different control signals that govern meal initiation, the maintenance of eating through intrameal control mechanisms, meal-ending satiation and intermeal satiety (e.g., 28). Each one of these has to be considered a single behavior and their physiological controls may act independently. Therefore, signals that in pharmacological trials have been shown to interact, i.e. that (1) they produce a more potent effect on food intake than each signal alone or that (2) one of the signals reduces the effect of that induced by the other, may not necessarily interact under physiological conditions, especially if they govern different behaviors within the overall control of food intake. Therefore, one has to differentiate between physiological mechanistic interaction of controls and the effect of combination therapy in pharmacological trials which may only rely on a single measured outcome, i.e. food intake.

Nevertheless, it seems very likely that combination therapies for obesity may have the same advantages of increased clinical potency and decreased side effects that have been demonstrated in many other areas of pharmacological therapeutics. Therefore, the study of interactions is an important area regarding their therapeutic potential. Basic research in this direction is relatively well advanced only in the case of CCK, which has been reported to functionally interact with several other peripheral signals that control
eating, e.g. amylin, estradiol, gastric load, glucagon, leptin and insulin (e.g., 5,6,19,22,34). With the exception of glucagon, all these interactions are synergistic i.e., eating was further decreased when CCK and the other signal were applied simultaneously as compared to CCK alone. Very much less is known about mechanistic versus functional interactions. The synergistic interaction between CCK and amylin may reflect a necessary part of CCK signaling because (1) amylin antagonists attenuated CCK’s anorectic action in rats (17) and (2) the anorectic effect of CCK was almost completely abolished in the complete absence of endogenous amylin in knockout mice and was rescued by small doses of amylin (19). These mechanistic interactions are perhaps more relevant to physiology than to pharmacology.

Insulin and leptin appear to act by increasing the sensitivity of the brain to CCK as meal-generated signals contributing to meal-ending satiation (21,30,33). Therefore, the integration of these messages within the brain including the signals reflecting body adiposity contributes to the sensation of satiation at meal termination. Theoretically, when an individual is underweight, the reduced adiposity signal allows larger meals to be consumed until weight is restored and vice versa.

Over the last two years, the group by Hubert Mönnikes and colleagues published two interesting papers on the pharmacological interaction of the functional antagonist to leptin and insulin, i.e. ghrelin, with the satiating peptides CCK (9), bombesin (BB) and amylin (8). Kobelt et al. (9) found that subthreshold doses of CCK abolished the orexigenic effect of ghrelin when co-administered intraperitoneally. These experiments
were complemented by immunohistochemical studies of expression of c-Fos protein. Ghrelin induced a strong increase in c-Fos expression in the hypothalamic arcuate (ARC) and paraventricular nuclei (PVN), but not in the nucleus of the solitary tract (NTS). CCK, on the other hand, induced c-Fos in the NTS and the PVN, but not in the ARC. CCK, however, completely reversed the ghrelin-induced c-Fos formation in the ARC.

In the latest paper by Mönninger and colleagues (see page XX of this issue), the authors extend their previous study on CCK and ghrelin to investigate now the possible interaction between BB and ghrelin, and amylin and ghrelin, respectively. This paper hence deals with an almost forgotten peptide because BB and its mammalian counterparts, gastrin-releasing peptide and neuromedin B, have not seen much interest over the last few years. One reason for this relative lack of interest may arise from some uncertainty about the true site of action (peripheral or central) and the receptors involved in BB’s anorectic response (33). In any event, the re-emerging interest in the stomach as a site of important controls of eating such as ghrelin may have led to the renewed interest in BB. At the same time, it would have been useful if the authors had verified their results with mammalian members of the bombesin family of peptides.

The other player in the current paper by Mönninger and colleagues, amylin, is synthesized by the pancreatic B-cells and co-secreted with insulin. One of the best investigated functions of amylin is its role as a hormonal control of meal-ending satiation (11,14). The effects of peripheral amylin on eating seem to be mediated by amylin receptors in the AP (15,20,24), and vagal and non-vagal visceral afferents, in contrast to
mediating the anorectic effects of CCK and BB (22,31), do not seem to be involved (12,23).

Similar to the previous findings with CCK (9), Kobelt et al. (8) now report that subthreshold doses of BB blocked the orexigenic effect of ghrelin. In contrast to the previous results, however, BB only slightly reduced ghrelin-induced c-Fos in the ARC. Furthermore, although BB alone had no effect on c-Fos expression in the PVN, it markedly enhanced ghrelin-induced PVN c-Fos. Phenotyping of the neurons that were activated by ghrelin alone or by the combination of ghrelin and BB revealed that a considerable proportion of these neurons were positive for corticotropin-releasing factor (CRF) because approximately 50% of neurons were co-labeled for c-Fos and CRF. However, CRF positive neurons mainly seem to subserve other purposes because only about 20% of CRF neurons expressed c-Fos after ghrelin and BB.

No interaction between the feeding response to amylin and ghrelin was found. Further, amylin has no effect on the extent of c-Fos in the ARC or PVN. While amylin reduces fasting-induced c-Fos expression in the lateral hypothalamic area (LHA) of rats (24), it has not been tested whether this response is affected by ghrelin. Further, recent studies have shown that amylin, via an action in the AP, affects ghrelin release (35) but this was not the focus of the study by Kobelt et al. (8).

All in all, the two papers by Mönnikes and colleagues extend our knowledge in respect to the pharmacological interaction of peptides that regulate feeding behavior.
While in the case of CCK and amylin, the papers add up to the existing literature, this is one of the very few studies investigating the relationship between members of the BB family of peptides and other peptidergic or non-peptidergic controls of food intake (e.g., 1). It seems likely that depending on the peptides, different specific neuronal networks are involved in the interactions, and this is nicely exemplified by the c-Fos studies indicating that ghrelin and BB interact in the PVN, and that ghrelin and CCK interact in the ARC. The negative data on a possible interaction between ghrelin and amylin suggest that interactions between ghrelin and CCK or ghrelin and BB, respectively, are specific and not just the sum of individual effects.

Amylin, BB and CCK all elicit a positive c-Fos response in the NTS, the lateral parabrachial nucleus (lPBN) and the central nucleus of the amygdala (CeNA) (10,24,25). What remains unknown is whether the peptides activate different cell groups within the NTS or different projections from NTS to the hypothalamus. To find this out would e.g. require phenotyping of the NTS neurons defining the different neurotransmitters that may mediate the effects of the different peptides. For example, whereas CCK satiation involves the hypothalamic serotoninergic system, the dopaminergic and histaminergic systems have been implicated in amylin signaling (13,16,18,29).

The studies like Kobelt et al.’s focus the attention on the crucial importance of identifying the specific neural projections from the NTS to hypothalamic nuclei but also vice versa (3). Combinations of extensive phenotyping of neurons might allow bidirectional analysis for the connections between brainstem and hypothalamus. Studies
only relying on c-Fos cannot do this. Even though the authors concentrated more on hypothalamic rather than brainstem mechanisms, the study of satiating peptides such as CCK, BB and amylin and their interaction with other hormones should also focus on interactions within the brainstem because of its importance for meal size control (7).

Studies based on c-Fos response face the inherent problem that c-Fos cannot provide information about neuronal inhibition. This shortcoming can e.g. be partly overcome by combining the c-Fos technique with appropriate experimental designs. The fasting-induced c-Fos response in specific hypothalamic nuclei is e.g. reversed by refeeding the animals, but also specifically by certain meal-related peptides such as shown for amylin in the LHA (24). Another obvious problem of c-Fos staining is that it is unable to yield information regarding the function of signals associated with neuronal activation in a certain brain area. At first sight, it seems unlikely that the increase in PVN c-Fos induced by ghrelin and BB occurs in the same neurons and hence relate to the same function because ghrelin’s and BB’s effects on feeding are opposite. Mönnikes and colleagues speculate, however, that this finding may indicate that ghrelin activates its own counterregulatory mechanism to limit the amount of food intake, and that this mechanism may be enhanced by BB via CRF neurons.

This also brings back the issue raised before about the difference between physiological control mechanisms of multiple behaviors involved in food intake and pharmacological interaction. In other words, while ghrelin has been hypothesized to be one of the factors leading to meal initiation (4), CCK, BB and amylin are all thought to
contribute to the control of meal size by acting as meal-ending, satiating peptides (33). Hence, specific neurons identified by a positive c-Fos response may be involved in different behaviors, and the specific functional correlate being associated with this activation may e.g. depend on the temporal pattern of activation, the metabolic context and neuronal activation in other brain areas.

As mentioned, extensive phenotyping of the neurons involved in the peptides’ effects in different brain regions and co-localization of c-Fos expression with hormone receptors will help to delineate the exact pathways of hormone action and interaction. Obviously, if c-Fos expression induced by a certain peptide does not co-localize with the hormone receptor, it is very unlikely that this particular site of c-Fos expression represents the primary site of action. Therefore, c-Fos staining has to be combined with other techniques. Such combinations, i.e. lesioning studies (15,24,35), local hormone administration (20) and staining for the receptor protein (2) helped e.g. to delineate the AP as most likely site of amylin action (and interaction with ghrelin in respect to the regulation of gastric ghrelin release).

Open questions may be addressed in future experiments using new imaging techniques (e.g. molecular in vivo imaging). These new imaging studies on the mechanism of action and interaction of peptide hormones would largely benefit from the possibility to assess temporal aspects of hormone action because classical c-Fos studies have mostly been performed at a single time point and therefore cannot yield such information. Further, these techniques may allow delineating the bidirectional pathways
between brainstem and hypothalamus. Such studies performed in natural feeding situations would seem to be a logical sequel of the work by Kobelt et al. (8,9) to study the different roles that these hormones might subserve in the control of meal pattern. Hence, studies both at the behavioral and imaging level are warranted to understand fully if and how different peptide hormones interact and which physiological behavior they govern.

To summarize, the two studies published by Kobelt et al. provide important information regarding the interaction of ghrelin with CCK, BB and amylin. Like most of the interesting experiments, however, the data raise more new questions than they can answer. Therefore, they open up new fields of investigation that have to be pursued in order to better understand the complex central nervous system network involved in the control of food intake and ultimately body weight. This may eventually lead both to improved physiological understanding and improved pharmacotherapy for the treatment of obesity.

References


