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Interoceptive "satiety" signals produced by leptin and CCK

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ABSTRACT

The present studies assessed the extent to which the adiposity signal leptin and the brain–gut hormone cholecystokinin (CCK), administered alone or in combination, give rise to interoceptive sensory cues like those that are produced by a low (1 h) level of food deprivation. Rats were trained with cues arising from 1 to 24-h food deprivation as discriminative stimuli. For one group, 24-h food deprivation predicted the delivery of sucrose pellets, whereas 1-h food deprivation did not. Another group received the reversed deprivation level-sucrose contingency. After asymptotic performance was achieved, the effects of leptin and CCK on food intake and on discrimination performance were tested under 24-h food deprivation. In Experiment 1a, leptin administered into the third cerebroventricle (i3vt) at 3.5 or 7.0 μg doses had little effect, compared to saline on food intake or discriminative responding. In Experiment 1b, leptin (7.0 μg, i3vt) combined with CCK-8 (2 μg/kg, i.p.) reduced food intake significantly, but the findings indicated that CCK-8 alone produces interoceptive discriminative cues more like those produced by 1- than 24-h food deprivation. Experiment 2a tested rats with i.p. leptin (0.3 and 0.5 mg/kg). Although neither dose suppressed intake, the 0.3 mg/kg dose produced interoceptive cues like 1-h food deprivation. Experiment 2b tested two doses of CCK-8 (2 and 4 mg/kg, i.p.) and found significant intake suppression and generalization of discrimination with both doses of CCK-8. These findings suggest a role for both leptin and CCK in the production of sensory consequences that correspond to "satiety".

1. Introduction

Leptin and cholecystokinin (CCK) have each received a great deal of attention as neuropeptide signals that contribute to the inhibition of food intake [38,49]. Leptin is secreted in the periphery by adipose tissue in direct proportion to body fat mass and is detected in the brain by receptors located in hypothalamic and brainstem areas that are known to be involved with food intake [44,50]. Furthermore, administration of exogenous leptin directly into the ventricles of the brain produces a dose-dependent decrease in food intake [29,45,50]. On the other hand, animals that lack or are insensitive to this hormone are hyperphagic and gain weight [2]. Based primarily on these considerations, leptin is often described as a relatively long-term adiposity signal because it can provide information to the brain about the status of longer-term bodily energy stores.

CCK, which is secreted by the duodenum as a response to nutrients entering the gut, is widely held to be a short-term, meal-related, inhibitory signal [37,38]. This view is supported

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by findings that administration of exogenous CCK-octapeptide (CCK-8) suppresses food intake in a dose dependent manner [28,33], whereas food intake is increased by antagonists of the CCK receptor subtype (CCK-A) that appears to mediate the suppressive effects of CCK agonists on feeding [3,8,13]. Furthermore, Otsuka Long Evans Tokushima Fatty (OLETF) rats that lack the CCK-A receptor are spontaneously hyperphagic, obese, and insensitive to the intake suppressive effect of exogenous CCK-8 [7].

Identifying the physiological events that are involved with intake inhibition is only part of the problem faced by researchers who seek to explain the ability of animals to match their energy intake to their needs for energy. The question of *how* such events function to suppress appetitive (e.g., responses that enable animals to obtain food) and consummmatory (e.g., eating) behavior must also be addressed. Leptin and CCK may suppress intake by participating in a variety of processes which are themselves complex. For example, either or both peptides could reduce food intake through their effects on (a) nonspecific behavioral deactivating mechanisms such as those involved with arousal or malaise [14,20,23,34]; (b) the hedonic properties of orosensory stimulation produced by eating [30,46]; and (c) the rewarding postingestive after-affects of intake [26,32,43]; (d) the generation of interoceptive ''satiety signals (e.g., ''fullness'') that inform animals about their current state of energy balance [6,27] and may enable them to anticipate the orosensory or postingestive consequences of eating in advance of actual contact with food [19].

The purpose of the present research is to evaluate this latter possibility. That is, our goal is to study whether or not exogenous leptin and CCK, administered separately or in combination, give rise to interoceptive satiety stimuli like those produced by a recent period of ad lib feeding. To achieve this goal, we employed what is known as a ''deprivation intensity discrimination design'' [15–18]. With this design, rats are given brief training sessions under irregularly alternating conditions of 1 and 24-h of food deprivation. For one group (Group 1+), sucrose pellets are delivered at the end of each session that is conducted under 1-h, but not 24-h, food deprivation. Another group (Group 24+) is trained with the opposite deprivation level-sucrose pellet contingency. The emergence of more conditioned responding (as indexed by interruption of a photobeam located in the recessed food magazine) when the rats are under their rewarded compared to their nonrewarded food deprivation level serves as the index of discrimination learning.

After asymptotic discrimination performance is achieved by both groups, the effects on conditioned responding of leptin and CCK are compared to saline when the rats are 24-h food-deprived. If the interoceptive cues produced by a peptide are no different than those produced by saline, then discriminative responding for rats in both Groups 1+ and 24+ should not differ dependent on test treatment. That is, consistent with their training histories, Group 1+ should respond less than Group 24+ whether testing is with a peptide or with saline. However, to the extent that treatment with a peptide gives rise to interoceptive cues that generalize to cues accompanying 1-h food deprivation, rats in Group 1+ should show more appetitive responding and rats in Groups 24+ should show less appetitive responding when tested following peptide, compared to saline, administration.

An important feature of this design is that it permits assessment of the interoceptive stimulus properties of leptin and CCK under conditions where the effects of those manipulations on the taste of food and on the rewarding postingestive consequences of eating are eliminated. These effects are eliminated because the rats have no opportunity to taste or eat food for 24-h prior to or during generalization test sessions. Furthermore, with this design, any nonspecific behavioral activating or deactivating effects of each peptide can also be evaluated. For example, to the extent that a peptide treatment produces interoceptive cues similar to 1-h food deprivation, appetititve conditioned responding would be expected to both increase (for Group 1+) and to decrease (for Group 24+) relative to saline, dependent on whether 1-h food deprivation cues signaled reward or nonreward during original training. This outcome would be difficult to explain in terms of any nonspecific effects of peptide treatment. Thus, unlike most previous studies, the present experiments are able to differentiate the potential effects of leptin and CCK on the generation of satiety signals, from their potential effects on taste, postingestive reward, and nonspecific behavioral deactivation.

2. Experiment 1a

2.1. *Introduction*

Experiment 1a assessed the degree to which third cerebroventricular (i3vt) infusions of leptin give rise to interoceptive stimulus consequences similar to those accompanying 1-h food deprivation. The experiment was conducted according to the following basic schedule: the rats were assigned to two groups for deprivation intensity discrimination training. Rats in Group 24+ received sucrose pellets at the conclusion of sessions when they were 24-h food deprived and received no pellets at the end of sessions conducted under 1-h food deprivation. When asymptotic discrimination performance was achieved by both groups, training was suspended. All rats then had surgery to implant cannula in the third cerebroventricle of the brain. Following recovery from surgery, the rats were given additional training sessions to return deprivation intensity discrimination performance to presurgical levels. After asymptotic discrimination was reinstated, each Group 24+ and 1+ were further subdivided for subsequent generalization testing. Half of the rats in each group were tested with a 0.35 μg i3vt dose of leptin on one session and with an equal volume of isotonic saline on second session, with order counterbalanced. The remaining rats in each group were similarly tested with a 0.7 μg, i3vt dose of leptin and saline. All test sessions took place when the rats were 24-h food deprived. The leptin doses chosen were shown in a previous study to be within a range that produced food intake suppression in a dose dependent manner in nondeprived rats within 1–2 h following i3vt infusion [22]. Leptin and saline injections took place approximately 1-h prior to the beginning of each test session. Food intake was measured at 1 and 22-h after each test session.