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RAPID COMMUNICATION

The 5-HT_{1A} Agonist 8-OH-DPAT Attenuates the Satiating Action of Cholecystokinin

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POESCHLA, B., J. GIBBS, K. J. SIMANSKY AND G. P. SMITH. *The 5-HT_{1A} agonist 8-OH-DPAT attenuates the satiating action of cholecystokinin.* PHARMACOL BIOCHEM BEHAV 42(3) 541-543, 1992.—To investigate the dependence of the satiating action of cholecystokinin (CCK) on serotonergic action at central 5-HT receptors, we examined the effect of systemic pretreatment with 8-OH-DPAT (a 5-HT_{1A} agonist that decreases central 5-HT synthesis and release via an action at somatodendritic autoreceptors in the brainstem raphe) on the suppression of food intake induced by systemic administration of cholecystokinin octapeptide (CKK-8). 8-OH-DPAT significantly attenuated the satiating action of CKK-8. This result is consistent with the hypothesis that peripherally acting CCK recruits central serotonergic processes to elicit normal satiety.

Brain-gut peptides Brain-gut interactions Cholecystokinin Control of food intake 5-HT_{1A} receptors 8-OH-DPAT Satiety Serotonin

STALLONE and her colleagues (20) recently showed that the satiating effect of systemically administered cholecystokinin octapeptide (CCK-8) was attenuated by metergoline, a 5-HT_1/5-HT_2 receptor antagonist. Subsequently, Ritter et al. (15) and Poeschla et al. (14) found that this reduction in the satiating potency of CCK-8 could be obtained with 5-HT_1/5-HT_2 antagonists, but not with antagonists selective for 5-HT_2 or 5-HT_3 receptor subtypes. These results suggest that the satiating effect of peripherally administered CCK-8 depends upon activation of 5-HT_1 receptor subtypes.

Since peripherally administered CCK-8 does not cross the blood-brain barrier (12), and since its satiety action is blocked by lesion of afferent fibers of the abdominal vagus nerve (18), the satiating effect of peripherally administered CCK-8 must be initiated by activating CCK receptors in the abdomen. The attenuation of this peripherally initiated satiating effect of CCK-8 by 5-HT_1 antagonists could be due to a peripheral or central action of the antagonist. We hypothesize that central action of the 5-HT_1 antagonists is critical on the basis of the following indirect evidence.

First, the reductions in food intake produced by peripherally administered CCK-8 (1) and by centrally administered 5-HT—applied to the medial hypothalamus (17)—share behavioral specificity: In each case meal size is decreased but latency to eat is not. Second, recent work by Hutson and his colleagues (10) with 5-HT agonists suggests that hypothalamic control of food intake involves activation of 5-HT_1 receptor subtypes—subtypes identified by Ritter et al. (15) and Poeschla et al. (14) as necessary for the full satiating effect of systemically administered CCK-8.

Ascending serotonergic axons in the brain derive from groups of cell bodies located in the dorsal and median raphe nuclei. 5-HT_{1A} autoreceptors have been identified on these cell bodies and their dendrites by autoradiography (7,13,22,23) and by immunohistochemistry (19). Activation of these autoreceptors by 5-HT_{1A} agonists such as 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) has a hyperpolarizing effect, decreasing the spontaneous firing rate of raphe neurons, and decreasing 5-HT synthesis and release (5,6,21).

Systemically administered 8-OH-DPAT produces hyper-

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phagia (4), and does so with greater efficacy in fully satiated than partially satiated rats (3). This hyperphagic effect is due to activation of 5-HT_{1A} receptors (9) and has been localized by microinfusion studies to an action at cell body autoreceptors in the dorsal and median raphe nuclei (2,8).

To further test the hypothesis that the satiating action of systemically administered CCK-8 depends upon intact functioning of central serotonergic systems, we examined the effect of systemically administered 8-OH-DPAT on the suppression of food intake produced by CKK-8 in rats.

METHOD

Ten male Sprague-Dawley rats initially weighing 200–250 g were housed individually in stainless steel cages in a room with a 12-h light-dark cycle (lights on at 0430 h). They had continuous access to a standard, nutritionally complete, pelleted laboratory diet (Purina) except for 3 h of food deprivation daily, followed by a 30-min test meal of the same diet in powdered form. Water was always available. The test meal was presented in ceramic bowls 1 h before dark; spillage was collected and returned to the bowls, and food intakes were measured to 0.1 g. The animals were habituated to this feeding regimen, and to vehicle injections, for several weeks prior to these experiments. Baseline intakes were stable (3.9 ± 0.1 g; $n = 5$ test days over a period of 5 weeks).

The hydrobromide salt of 8-OH-DPAT (Research Biochemicals, Natick, MA) was dissolved in 0.9% saline and injected subcutaneously, in a volume of 1 ml/kg 1 h prior to the test meal. The sulfated COOH-terminal octapeptide of CCK (CCK-8, a gift of Bristol-Meyers-Squibb Pharmaceutical Research Institute) was dissolved in 0.9% saline and injected IP, in a volume of 1 ml/kg, immediately prior to presentation of the test meal.

Treatments were administered by a repeated measures design, with all animals receiving the same treatment on a given test day. At least 5 days separated successive administrations of 8-OH-DPAT. Data were analyzed by three-way analysis of variance (ANOVA) with repeated measures, with CCK-8, 8-OH-DPAT, and dose as factors. The post-hoc test used was Duncan's multiple range test. The significance level was set at $p < 0.05$ for each of the two doses of 8-OH-DPAT used.

RESULTS

Both doses of 8-OH-DPAT significantly attenuated the suppression of food intake induced by CCK-8, and did not affect food intake when given alone (see Table 1). There was a trend toward greater attenuation of the effect of CCK-8 by the larger dose of 8-OH-DPAT, but this difference was not statistically significant.

At the larger dose used (120 μg/kg), 8-OH-DPAT produced a short-lived behavioral syndrome: flat body posture, arched neck, headweaving, and gaping mouth. This syndrome, which resembles a previously described 8-OH-DPAT-induced serotonin syndrome (4), disappeared within 45 min, that is, at least 15 min prior to presentation of the test meal in all subjects. None of these effects was apparent after the smaller dose of 8-OH-DPAT. Since both doses attenuated the satiating action of CCK-8, the occurrence of the behavioral syndrome after the larger dose was not necessary for the attenuation of the effect of CCK-8.

DISCUSSION

The attenuation of the satiating action of peripherally administered CCK-8 by 8-OH-DPAT is consistent with our hypothesis that central serotonergic systems play a critical role in translating peripheral signals generated by CCK into the behavioral responses associated with satiety.

Hutson and his colleagues (10) have suggested a scheme that links raphe control of serotonin release (via 5-HT_{1A} autoreceptors) with inhibitory control of feeding in the paraventricular nucleus (via postsynaptic 5-$HT_{1B/1C}$ receptors). Since we have reported that the satiating action of systemically administered CCK depends upon activation of 5-HT_1 receptors (see introductory section), it is possible that the presynaptic action of 8-OH-DPAT attenuated the satiating effect of CCK-8 by indirectly reducing serotonergic activity at postsynaptic 5-HT_1 receptors. This hypothesis is consistent with the finding of Schwartz et al. (16) that systemic administration of 8-OH-DPAT produced a 72–73% decrease in extracellular serotonin (measured by in vivo microdialysis) in the medial and lateral hypothalamus and with the finding of Hutson et al. (8) that the smaller dose of 8-OH-DPAT used in our experiments (60 μg/kg, SC) significantly decreased the 5-HIAA/5-HT ratio in the hypothalamus. It should be emphasized, however, that 8-OH-DPAT produces widespread changes in brain serotonin metabolism in extrahypothalamic regions, for example, cortex, midbrain, pons, and medulla. In the latter two regions the changes last up to 120 min following SC injection and this is similar to the time course over which the same dose of the drug enhances feeding (8).

TABLE 1

THE EFFECT OF 8-OH-DPAT ON THE SATIATING ACTION OF CCK-8

	Treatments			
Dose of 8-OH-DPAT	Vehicle + Vehicle	Vehicle + CCK-8	8-OH-DPAT + CCK-8	8-OH-DPAT + Vehicle
60 μg/kg	3.6 ± 0.4	1.1 ± 0.3*	1.9 ± 0.4†	3.4 ± 0.5
120 μg/kg	4.2 ± 0.5	1.0 ± 0.3*	2.5 ± 0.4†	3.9 ± 0.4

Numbers represent mean 30-min food intakes (g ± SEM). The dose of CCK-8 was 6 μg/kg. Statistical comparisons: *$F(1, 9) = 60.7$, $p < 0.01$, CCK-8 + vehicle vs. vehicle + vehicle; †$F(1, 9) = 10.73$, $p < 0.01$, CCK-8 + 8-OH-DPAT vs. CCK-8 + vehicle.

Although we have focused on a role for the brain in interpreting our results, the site of interaction between peripherally administered CCK-8 and serotonergic systems affected by 8-OH-DPAT could be peripheral, not central: Kirchgessner and colleagues (11) have recently reported the existence of 5-HT_{1A} sites which bind 8-OH-DPAT located on intrinsic neurons of the gastrointestinal tract. Thus, experiments in which 8-OH-DPAT is microinjected directly into the brain regions containing serotonergic cell bodies in the brain are necessary for testing more conclusively the roles of specific central serotonergic pathways in the satiating action of CCK-8. Injecting 5-HT_1 antagonists into the terminal fields innervated by these pathways could provide important evidence for our hypothesis that peripherally acting CCK recruits central serotonergic processes to elicit normal satiety.

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