Pergamon

Pharmacology Biochemistry and Behavior, Vol. 48, No. 4, pp. 1019–1024, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)E0016-B

BRIEF COMMUNICATION

Evidence for the Contribution of CCK_B Receptor Mechanisms to Individual Differences in Amphetamine-Induced Locomotion

G. A. HIGGINS,* T. L. SILLS,† D. M. TOMKINS,* E. M. SELLERS*‡ AND F. J. VACCARINO†§[1]

Addiction Research Foundation and Departments of Pharmacology, †Psychology, ‡Medicine, and §Psychiatry, University of Toronto, 100 St. George Street, Toronto, Ontario, Canada M5S 1A1

Received 26 July 1993

HIGGINS, G. A., T. L. SILLS, D. M. TOMKINS, E. M. SELLERS AND F. J. VACCARINO. *Evidence for the contribution of CCK_B receptor mechanisms to individual differences in amphetamine-induced locomotion.* PHARMACOL BIOCHEM BEHAV **48**(4) 1019–1024, 1994. – Recent evidence shows that rats exhibit individual differences in their locomotor response to amphetamine (AMP). Moreover, evidence has accumulated showing that high-AMP responders exhibit more mesolimbic dopaminergic (DAergic) activation in response to AMP treatment than low-AMP responders. Cholecystokinin (CCK) is a peptide that is colocalised with mesolimbic DA and exerts complex modulatory actions on DA function. Two CCK receptor subtypes have been identified and selective antagonists have been developed. To examine the possible contribution of endogenous CCK mechanisms to individual differences in responsivity to AMP treatment, male Wistar rats were divided into low- and high-AMP responders based on a median split of their locomotor response to AMP and the effects of the selective CCK antagonists L365-260 (CCK_B; 0.01, 0.1, 0.5 mg/kg; n = 16) and devazepide (CCK_A; 0.001, 0.01, 0.1 mg/kg; n = 23) were determined. Results showed that L365-260 (0.1 mg/kg) potentiated AMP-induced hyperactivity in low-AMP responders but did not affect AMP-induced hyperactivity in high-AMP responders. Devazepide was without effect in both groups of animals. This pattern of results suggests that CCK_B, but not CCK_A, receptor mechanisms contribute to interindividual variation in responsivity to AMP.

Amphetamine Locomotion Cholecystokinin Antagonists Devazepide L365-260 Individual differences Rat

THE peptide cholecystokinin (CCK) exerts important neuromodulatory effects in both the CNS and periphery (47). Current research suggests that these effects are mediated via two distinct receptor subtypes, termed CCK_A (alimentary) and CCK_B (brain) (14,15,27). As the nomenclature suggests, it is the CCK_A receptor that is the predominant form in the periphery, although there is a limited distribution of this subtype within the CNS (14,15). The CCK_B receptor, on the other hand, is widely distributed throughout most brain regions of various mammalian species (14,15). Selective agonists and antagonists have been developed for both receptor subtypes, with perhaps the most widely used antagonists presently being the substituted benzodiazepines, devazepide (formerly MK329, L364-718) (3,7) and L365-260 (24), which show approximately one hundredfold selectivity for CCK_A and CCK_B receptors, respectively (3,7,15,24).

Based on the observation that CCK and dopamine (DA) are colocalised within certain neurons comprising the A10 mesolimbic pathway (17,18,24,36,37), there has been extensive research examining the interaction between these neurotransmitters at both the biochemical (1,9,25,42–44) and behavioral (4–6,11,23,29,38,40,45,46) level. It has been shown

[1] Requests for reprints should be addressed to F. J. Vaccarino, Department of Psychology, University of Toronto, 100 St. George Street, Toronto, Ontario, Canada M5S 1A1.

from such studies that CCK serves both a facilitatory and suppressant role on DA function within the mesolimbic system, and in particular within the nucleus accumbens (Acc). For instance, CCK injected into the medio-caudal region of the Acc has been reported to potentiate behaviors associated with activation of Acc DA systems (5,6,23,29,38) and to stimulate DA release from brain slices prepared from this region (25,42). Pharmacological evidence is beginning to converge, and it suggests that this facilitatory role for CCK is mediated via the CCK_A receptor subtype (4,23,25,29,42). In contrast, injections of CCK into more rostral areas of the Acc appear to inhibit DA- and amphetamine-induced hyperactivity (4,5, 38,46) and to reduce DA release from rostral Acc brain slice preparations (1,25). Moreover, evidence suggests that these suppressant effects of CCK are mediated via the CCK_B subtype (1,4,25).

It is well established that *d*-amphetamine (AMP) produces an increase in locomotor behavior and that this effect is mediated by an enhancement of DA release from neurons of the mesolimbic pathway. More specifically, the Acc has been identified as the critical terminal region for the mediation of this response [see (22,39) and refs. therein]. The role of DA in AMP-induced locomotor activity recently has been extended to account for individual differences in this behavior. It has been demonstrated that rats showing a high level of locomotor activation to AMP have higher levels of Acc DA than animals showing lower levels of activation (30,31).

In light of the DA–CCK interaction found within the Acc, it is possible that endogenous CCK contributes to the expression of AMP-induced behaviors and, possibly, to the manifestation of individual differences in responsivity to AMP treatment. To examine this possibility, the present study investigated the effects of the CCK antagonists devazepide and L365-260 on a behavior that requires the integrity of Acc DA function, namely, AMP-induced hyperactivity. This study is especially warranted because the recent microdialysis studies of Hurd et al. (21) show enhanced DA and CCK release within the rat Acc following AMP pretreatment. This further suggests a potential involvement of endogenous CCK systems in some of the behavioral effects to AMP.

The present study assessed the effects of devazepide and L365-260 on the locomotor activity elicited by a relatively low dose of AMP (0.25 mg/kg) administered to rats. The doses of CCK antagonists used in these studies were based on previously published work (13). A within-subjects design was used for these studies in view of the marked individual differences between rats in their locomotor response to systemic injections of AMP (19,30–32).

METHOD

Animals and Housing

Male Wistar rats (Charles River, Quebec, Canada) weighing approximately 300 g at the start of the study were used. Rats were individually housed in wire mash cages in a temperature- and light-controlled environment (lights on 0700–1900 h). All subjects had ad lib access to food (Purina rat chow) and water except during testing. Activity testing was conducted between 1000 and 1300 h. A 7-day period was allowed between arrival and commencement of behavioral testing.

Locomotor Activity Apparatus

The locomotor activity system consisted of 16 cages, each measuring 20 × 25 × 36 cm with a wire mesh floor. Two infrared photocell beams were situated across the long axis of the cage 2 cm above the floor. The locomotor activity measurements were based on the total beam interruptions that were collected and totaled every 5 min on an IBM personal computer located in an adjacent room.

Locomotor Testing Procedure

Initially, the rats were placed in a designated locomotor activity cage for two 3-h periods on consecutive days to habituate them to the apparatus. The following day each rat then entered a six-cycle protocol with each cycle 3 h in duration and conducted at 72-h intervals. On the first and last cycle, each rat received a vehicle injection at $t = 0.5$ h and $t = 1$ h; locomotor activity was then monitored for the subsequent 2 h. During the middle four cycles, each rat was injected with either one of three doses of CCK antagonist or saline vehicle at $t = 0.5$ h always followed by AMP (0.25 mg/kg) at $t = 1$ h. Again, locomotor activity was recorded for the subsequent 2 h. The order of treatments was counterbalanced according to a 4 × 4 Latin square design.

One possible confound in the present repeated-measures design using AMP is that of sensitization [see Kalivas and Stewart (22) for recent review]. To control for this, 10 rats were administered the identical protocol to that above with the exception that saline was administered in the place of the CCK antagonists.

Drugs and Injections

Amphetamine sulphate (Bureau of Dangerous Drugs, Ottawa, Canada) was dissolved in saline; the final drug concentration refers to the salt. Devazepide and L365-260 (Merck Sharpe and Dohme, Harlow, UK) were initially mixed with a small (one-tenth of final volume) volume of solvent that was composed of acetonitrate : methanol : water in the ratio 1 : 1 : 2. This solution was then brought up to final volume with saline and sonicated for 5 min. The CCK antagonist vehicle was a 1 : 10 dilution of solvent in saline. It is important to note that, at this concentration, no irritation around the injection site was noted following repeated (six times) solvent injection. However, at lower dilution levels (i.e., 1 : 2, 1 : 5), there were signs of tissue necrosis and irritation following repeated injections of this solvent. All drugs were injected SC in a dose volume of 2 ml/kg. Both CCK antagonists or their vehicle were always administered 30 min prior to AMP.

Analysis of Data

All data are expressed as mean ± SEM. Locomotor activity data were statistically analyzed with a repeated-measures one (treatment)- or two (treatment × time)-factor analysis of variance (ANOVA) followed by post hoc Tukeys or contrast tests where appropriate. The accepted level of significance was $p < 0.01$.

RESULTS

Amphetamine (0.25 mg/kg, SC) produced a reliable increase in locomotor activity under the present experimental conditions (Figs. 1A and 2A). There was no significant difference with respect to saline pretreatment at test sessions 1 and 6; consequently, the data were collapsed across these two sessions to yield the saline score. Moreover, the locomotor response to AMP did not change across the test sessions, $F(3, 27) = 0.512$, NS.

In accordance with previous research (19,30,31), we ob-

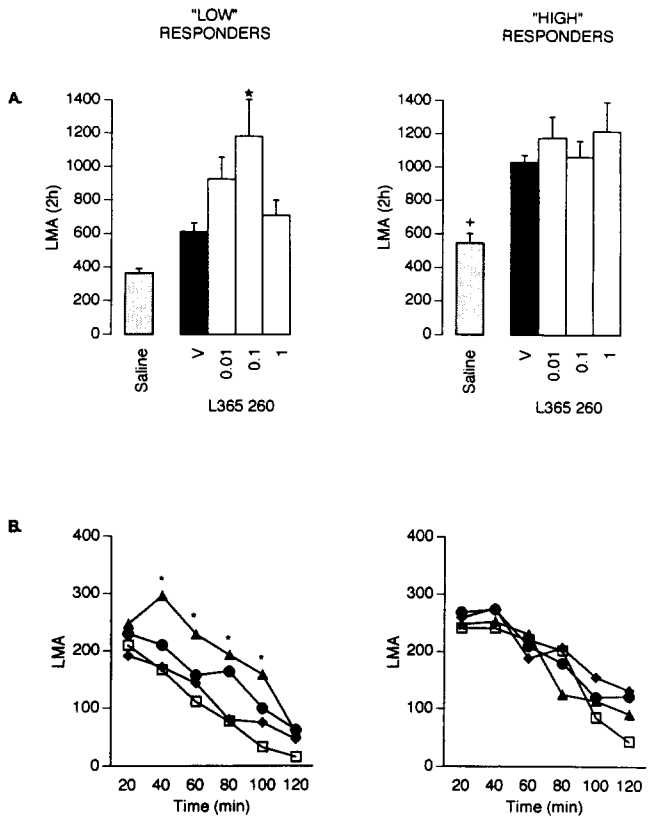

FIG. 1. Effect of L365-260 on AMP-induced hyperactivity in low and high responders (see text for details). (A) Effect of L365-260 (open bars) or vehicle (shaded bar) pretreatment on AMP-induced hyperactivity (0.25 mg/kg) recorded during the 2-h test session. ★$p < 0.01$ vs. low vehicle/AMP (V) group (Tukey's test). Saline (stippled bar) group represents the mean locomotor activity score recorded on the first and sixth cycle where the rats only received saline injections. +$p = 0.01$ vs. respective saline measure in low-AMP group (unpaired t-test). (B) Temporal analysis of the effect of L365-260 at 0.01 mg/kg (●), 0.1 mg/kg (▲), 1 mg/kg (♦), and vehicle (□) pretreatment on AMP-induced hyperactivity in low and high responders. ★$p < 0.05$ vs. vehicle pretreatment (contrast test).

served marked individual differences in the magnitude of locomotor change following AMP pretreatment. We therefore performed a median split of the animals on the basis of their AMP response following saline pretreatment. Thus, two groups were established, a low-AMP group and a high-AMP group. In the case of L365-260, the high-AMP group ($n = 8$) had a mean response across the 2-h test session of 1032 ± 44 and the low-AMP group ($n = 8$) had a mean response of 611 ± 52. In the low group, ANOVA revealed a significant effect of treatment, $F(3, 21) = 5.1$, $p < 0.01$, with post hoc testing indicating a significant potentiation of the AMP response following pretreatment with 0.1 mg/kg L365-260 (Fig. 1A). Further analysis revealed a significant main effect of time, $F(5, 168) = 25.2$, $p < 0.01$, and treatment, $F(3, 168) = 5.5$, $p < 0.01$, whereas the treatment × time interaction was of borderline significance, $F(15, 168) = 1.7$, $p = 0.056$. Contrast tests between means indicated that at the 0.1-mg/kg dose, L365-260 potentiated the AMP response at time bins 40–100 min (Fig. 1B). In the high-AMP group, there was no significant effect of treatment, $F(3, 21) = 0.5$, NS, a finding confirmed by subsequent analysis of the temporal data where a main effect of time, $F(5, 168) = 13.8$, $p < 0.01$, but not treatment, $F(3, 168) = 0.5$, NS, was recorded.

For devazepide, the high-AMP responders ($n = 11$) had a mean locomotor score of 1044 ± 142 and the low-AMP responders ($n = 11$) had a mean locomotor score of 533 ± 46. Following devazepide (0.001–0.1 mg/kg) pretreatment there was no effect against the AMP response in low- and high-AMP responders [low, $F(3, 40) = 0.3$, NS; high, $F(3, 40) = 0.4$, NS; Fig. 2A]. Further analysis revealed a significant main effect of time in both the low- and high-AMP responders [$F(5, 200) = 33.2$, $p < 0.001$, and $F(5, 200) = 43.8$, $p < 0.001$, respectively]. However, there was no significant effect of treatment [$F(3, 200) = 0.2$, NS, and $F(3, 200) = 0.4$, NS] or treatment × time interaction [$F(15, 200) = 0.5$ and $F(15, 200) = 0.5$) in either the low or high responders (Fig. 2B).

Of final note, comparison of the locomotor response following saline pretreatment revealed differences between the low- and high-AMP groups in both the L365-260 study [i.e., low vehicle = 364 ± 26; high vehicle = 547 ± 56; $t(14) = 2.96$, $p = 0.01$] and the devazepide study (i.e., low vehicle =

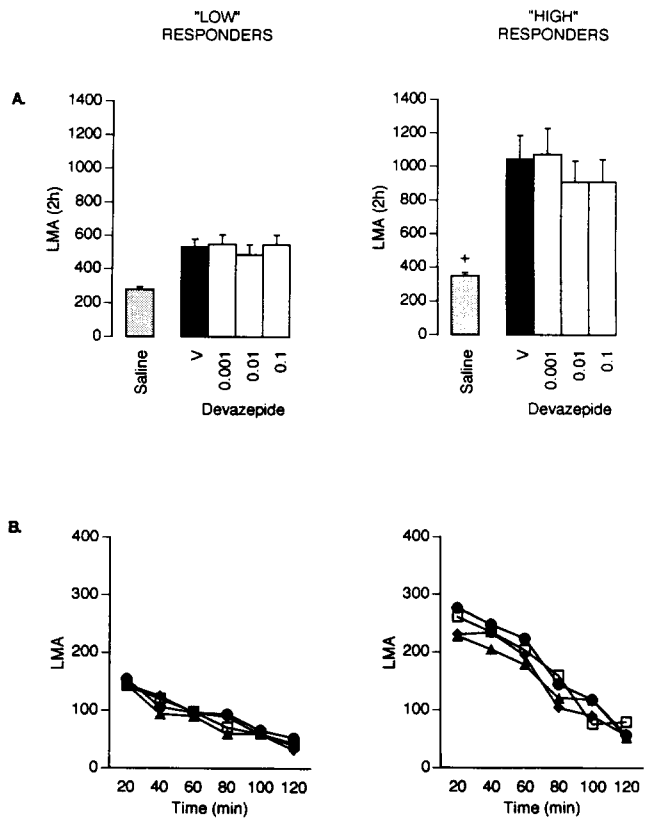

FIG. 2. Effect of devazepide on AMP-induced hyperactivity in low and high responders (see text for details). (A) Effect of devazepide (open bars) or vehicle (shaded bar) pretreatment on AMP-induced hyperactivity (0.25 mg/kg) recorded during the 2-h test session. Saline (stippled bar) group represents the mean locomotor activity score recorded on the first and sixth cycle where the rats only received saline injections. +$p < 0.01$ vs. respective saline measure in low-AMP group (unpaired t-test). (B) Temporal analysis of the effect of devazepide at 0.001 mg/kg (●), 0.01 mg/kg (▲), 0.1 mg/kg (♦), and vehicle (□) pretreatment on AMP-induced hyperactivity in low and high responders.

280 ± 16; high vehicle = 349 ± 18; $t(20) = 2.96, p < 0.01$]. In other words, animals from the high-AMP group showed a greater locomotor response following saline injection relative to their low-AMP counterparts (Figs. 1A and 2A).

DISCUSSION

In this study, we examined the effect of the CCK_A antagonist, devazepide, and the CCK_B antagonist, L365-260, on AMP-induced hyperactivity. In accordance with previous research, marked individual differences were seen between rats in their response to AMP. Based on previous research indicating that low and high responders differ in the level of DA function (31), we performed a median split of each group according to their response to AMP. It was found that although L365-260 had no effect in high-AMP responders, in the low group there was a marked potentiation of the hyperactivity. It was curious to note that this potentiation seemed biphasic, with enhancement at 0.1 mg/kg but not at 1 mg/kg L365-260. L365-260 did not effect locomotor activity in vehicle-pretreated rats, implying that the ineffectiveness of the 1-mg/kg dose in the AMP interaction study was not due to motoric impairment.

In a recent study in monkeys, Boyce et al. (2) also reported a steep dose–response curve for L365-260 effects on DA-mediated hyperlocomotion. Boyce et al. treated monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce a parkinsonian syndrome. They subsequently administered the DA agonists L-DOPA and (+)-PHNO to the MPTP monkeys and found a substantial increase in locomotor activity. Importantly, L-DOPA-induced hyperlocomotion was potentiated by pretreatment with 1.0 mg/kg L365-260, whereas 10 mg/kg L365-260 potentiated (+)-PHNO-induced hyperactivity. At no other dose was there an enhancement of the hyperactivity induced by the DA agonists. As well, devazepide was without effect under all conditions. Endogenous CCK, at the CCK_B receptor, may function to inhibit DA-mediated motor activity. This is in line with previous studies (5,38,46) showing that CCK antagonizes DA- and AMP-induced hyperactivity.

It is noteworthy that biphasic dose–response relationships have also been recorded for the inhibitory effects of CCK-8 or CCK-8S against apomorphine- and AMP-induced hyperactivity following Acc injection (45,46). Precisely what processes underlie this response profile are presently unclear, but it does suggest a functional complexity between Acc DA and CCK systems.

In contrast to L365-260, the CCK_A receptor antagonist devazepide failed to significantly affect AMP-induced locomotor activation in both low and high responders. These results suggest a relatively unimportant role for CCK_A receptors in the regulation of the motor response to AMP, and imply some specificity to the L365-260 response. Though the CCK_A receptor subtype may not contribute to the mechanism(s) regulating responsiveness to AMP treatment, this receptor subtype, but not the CCK_B subtype, has been shown to be critical to the expression of CCK-induced hypolocomotion. Thus, it has been shown that devazepide, but not L365-260, will block the hypolocomotion induced by both systemic and central CCK administration (16,28,35,41).

It is important to note that two important consequences of chronic AMP treatment that could have compromised a repeated-measures approach are sensitization [see Kalivas and Stewart (22) for recent review] and conditioning (12,26) to the hyperactivity. However, using a low AMP dose (0.25 mg/kg) administered at 72-h intervals, we failed to find any evidence for these phenomena. Thus, there was no significant change in the AMP response across test sessions, or to the saline response recorded prior to, and after, the four AMP treatment cycles.

Perhaps the most interesting aspect to this work, and one that is receiving increasing attention, is the individual differences seen between laboratory animals in their responding to drug reinforcers such as AMP and morphine (10,19,20,30–34). Piazza et al. (30) have provided evidence that in rats, the baseline level of locomotor activity is positively correlated with the animal's locomotor response to AMP and also the rate of acquisition to self-administer this substance. In the present study, we also found similar correlations between baseline activity and an AMP-induced hyperactivity, because rats identified as high-AMP responders showed a significantly greater locomotor response during habituation and to a saline injection in comparison to their low-AMP counterparts.

Precisely why animals should differ in their level of responding to AMP is likely to be due to a complex array of variables. However, studies do suggest that animals that show a greater propensity to acquire opioid or psychostimulant self-administration behavior, or exhibit enhanced locomotor activation to these drugs, may show biochemical markers indicative of enhanced mesolimbic DA function in comparison to those that do not (10,20,31). This DA system is presumably regulated by a variety of other neurotransmitter systems, including CCK and 5-HT; thus, it is feasible that differences in the functioning of these regulatory systems between animals could account for the observed neurochemical changes with respect to mesolimbic DA. In the present study, we found that pretreatment with the CCK_B antagonist L365-260 had no effect on the locomotor response to AMP in high responders, whereas in the low group activity was enhanced to a level seen in the high responders. Because activation of CCK_B receptors may suppress various aspects of Acc DA function (1,4,25,38), a possible explanation for the present findings is that low-AMP responders have a higher basal tone of CCK within the Acc that serves to dampen DA activity. Removal of this inhibitory component by application of a CCK_B antagonist may therefore enhance DA-related behavior. Clearly, more research is necessary to further examine such a hypothesis and we are currently investigating the effect of L365-260 pretreatment against feeding elicited by low doses of AMP. Like the hyperactivity response, AMP-induced feeding appears to be mediated via the Acc and also marked individual differences in this behavior may be seen between animals (8,33,34).

ACKNOWLEDGEMENTS

We would like to thank Merck Sharp and Dohme, Harlow, UK, for the generous gift of devazepide and L365-260. This research was supported by operating grants from MRC (Canada) and Ontario Mental Health Foundation to F.J.V.

REFERENCES

1. Altar, C. A.; Boyar, W. C. Brain CCKB receptors mediate the suppression of dopamine release by cholecystokinin. Brain Res. 483:321–326; 1989.

2. Boyce, S.; Rupniak, N. M. J.; Tye, S.; Steventon, M. J.; Iversen, S. D. Modulatory role of CCK-B antagonists in Parkinson's disease. Clin. Neuropharmacol. 13:339–347; 1990.

3. Chang, R. S. L.; Lotti, V. J. Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist. Proc. Natl. Acad. Sci. USA 83:4923–4926; 1986.
4. Crawley, J. N. Subtype-selective cholecystokinin receptor antagonists block cholecystokinin modulation of dopamine-mediated behaviors in the rat mesolimbic pathway. J. Neurosci. 12:3380–3391; 1992.
5. Crawley, J. N.; Hommer, D. W.; Skirboll, L. R. Topographical analysis of nucleus accumbens sites at which cholecystokinin potentiates dopamine-induced hyperlocomotion in the rat. Brain Res. 335:337–341; 1985.
6. Crawley, J. N.; Stivers, J. A.; Blumstein, L. K.; Paul, S. M. Cholecystokinin potentiates dopamine-mediated behaviors: Evidence for modulation specific to a site of coexistence. J. Neurosci. 5:1972–1983; 1985.
7. Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. Design of potent, orally effective, nonpeptidal antagonists of the peptide hormone cholecystokinin. Proc. Natl. Acad. Sci. USA 83:4918–4922; 1986.
8. Evans, K. R.; Vaccarino, F. J. Amphetamine- and morphine-induced feeding: Evidence for involvement of reward mechanisms. Neurosci. Biobehav. Rev. 14:9–22; 1990.
9. Fuxe, K.; Andersson, K.; Locatelli, V.; Agnati, L. F.; Hokfelt, T.; Skirboll, L.; Mutt, V. Cholecystokinin peptides produce marked reduction of dopamine turnover in discrete areas in the rat brain following intraventricular injection. Eur. J. Pharmacol. 67:329–331; 1980.
10. Glick, S. D.; Merski, C.; Steindorf, S.; Wang, S.; Keller, R. W.; Carlson, J. N. Neurochemical predisposition to self-administer morphine in rats. Brain Res. 578:215–220; 1992.
11. Heidbreder, C.; Gewiss, M.; De Mot, B.; Mertens, I.; De Witte, P. Balance of glutamate and dopamine in the nucleus accumbens modulates self-stimulation behavior after injection of cholecystokinin and neurotensin in the rat brain. Peptides 13:441–449; 1992.
12. Herz, R. S.; Beninger, R. J. Comparison of the ability of (+)-amphetamine and caffeine to produce environment-specific conditioning. Psychopharmacology (Berlin) 92:365–370; 1987.
13. Higgins, G. A.; Nguyen, P.; Sellers, E. M. Morphine place conditioning is differentially affected by CCK_A and CCK_B receptor antagonists. Brain Res. 572:208–215; 1992.
14. Hill, D. R.; Campbell, N. J.; Shaw, T. M.; Woodruff, G. N. Autoradiographic localization and biochemical characterization of peripheral type CCK receptors in rat CNS using highly selective nonpeptide CCK antagonists. J. Neurosci. 7:2967–2976; 1987.
15. Hill, D. R.; Woodruff, G. N. Differentiation of central cholecystokinin receptor binding sites using the non-peptide antagonists MK-329 and L-365,260. Brain Res. 526:276–283; 1990.
16. Hirosue, Y.; Inui, A.; Miura, M.; Nakajima, M.; Okita, M.; Himori, N.; Baba, S.; Kasuga, M. Effects of CCK antagonists on CCK-induced suppression of locomotor activity in mice. Peptides 13:155–157; 1992.
17. Hokfelt, T.; Rehfeld, J. F.; Skirboll, L. R.; Ivemark, B.; Goldstein, M.; Markey, K. Evidence for coexistence of dopamine and CCK in meso-limbic neurons. Nature 285:476–478; 1980.
18. Hokfelt, T.; Skirboll, L. R.; Rehfeld, J. F.; Goldstein, M.; Markey, K.; Dann, O. A subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: Evidence from immunohistochemistry combined with retrograde tracing. Neuroscience 5:2093–2124; 1980.
19. Hooks, M. S.; Jones, G. H.; Neill, D. B.; Justice, J. B. Individual differences in amphetamine sensitization: Dose-dependent effects. Pharmacol. Biochem. Behav. 41:203–210; 1991.
20. Hooks, M. S.; Jones, G. M.; Smith, A. D.; Neill, D. B.; Justice, J. B. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 9:121–128; 1991.
21. Hurd, Y. L.; Lindefors, N.; Brodin, E.; Brene, S.; Persson, H.; Ungerstedt, U.; Hokfelt, T. Amphetamine regulation of mesolimbic dopamine/cholecystokinin neurotransmission. Brain Res. 578:317–326; 1992.
22. Kalivas, P. W.; Stewart, J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res. Rev. 16:223–244; 1991.
23. Koshikawa, N.; Kikuchi de Beltran, K.; Saigusa, T.; Kobayashi, M.; Stephenson, J. D. Cholecystokinin octapeptide and caerulein injection into the dorsomedial nucleus accumbens potentiate apomorphine-induced jaw movements in rats. Eur. J. Pharmacol. 209:75–80; 1991.
24. Lotti, V. J.; Chang, R. S. L. A new potent and selective nonpeptide gastrin antagonist and brain cholecystokinin receptor (CCKB ligand: L-365,260. Eur. J. Pharmacol. 162:273–280; 1989.
25. Marshall, F. H.; Barnes, S.; Hughes, J.; Woodruff, G. N.; Hunter, J. C. Cholecystokinin modulates the release of dopamine from the anterior and posterior nucleus accumbens by two different mechanisms. J. Neurochem. 56:917–922; 1991.
26. Mazurski, E. J.; Beninger, R. J. Environment-specific conditioning and sensitization with (+)-amphetamine. Pharmacol. Biochem. Behav. 27:61–65; 1987.
27. Moran, T. H.; Robinson, P. H.; Goldrich, M. S.; McHugh, P. R. Two brain cholecystokinin receptors: Implications for behavioral actions. Brain Res. 362:175–179; 1986.
28. O'Neill, M. F.; Dourish, C. T.; Iversen, S. D. Hypolocomotion induced by peripheral or central injection of CCK in the mouse is blocked by the CCK_A receptor antagonist devazepide but not by the CCK_B receptor antagonist L-365,260. Eur. J. Pharmacol. 193: 203–208; 1991.
29. Phillips, G. D.; Westergreen, A.-L. M.; Robbins, T. W.; Everitt, B. J. Functional synergism within the ventral striatum between cholecystokinin and dopamine in the control over behavior by conditioned reinforcers. Psychopharmacology (Berlin) 6:115; 1992.
30. Piazza, P. V.; Deminiere, J. V.; Le Moal, M.; Simon, H. Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511–1513; 1989.
31. Piazza, P. V.; Rouge-Pont, F.; Deminiere, J. M.; Kharoubi, M.; Le Moal, M.; Simon, H. Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats predisposed to develop amphetamine self-administration. Brain Res. 567:169–174; 1991.
32. Segal, D. S.; Kuczenski, R. Individual differences in responsiveness to single and repeated amphetamine administration: Behavioral characteristics and neurochemical correlates. J. Pharmacol. Exp. Ther. 242:917–926; 1987.
33. Sills, T. L.; Baird, J. P.; Vaccarino, F. J. Individual differences in the feeding effects of amphetamine: Role of nucleus accumbens dopamine and circadian factors. Psychopharmacology (Berlin) 112:233–241; 1993.
34. Sills, T. L.; Vaccarino, F. J. Facilitation and inhibition of feeding by a single dose of amphetamine: Relationship to baseline intake and accumbens cholecystokinin. Psychopharmacology (Berlin) 105:329–334; 1991.
35. Smith, G. P.; Tyrka, A.; Gibbs, J. Type-A CCK receptors mediate the inhibition of food intake and activity by CCK-8 in 9- to 12-day-old rat pups. Pharmacol. Biochem. Behav. 38:207–210; 1991.
36. Studler, J. M.; Reibaud, M.; Tramu, G.; Blanc, G.; Glowinski, J.; Tassin, J. P. Distinct properties of cholecystokinin-8 and mixed dopamine-cholecystokinin-8 neurons innervating the nucleus accumbens. Ann. NY. Acad. Sci. 448:306–314; 1985.
37. Studler, J. M.; Reibaud, M.; Tramu, G.; Blanc, G.; Glowinski, J.; Tassin, J. P. Pharmacological study on the mixed CCK8/DA meso-nucleus accumbens pathway: Evidence for the existence of storage sites containing the two transmitters. Brain Res. 298:91–97; 1984.
38. Vaccarino, F. J.; Rankin, J. Nucleus accumbens cholecystokinin (CCK) can either attenuate or potentiate amphetamine-induced locomotor activity: Evidence for rostral-caudal differences in accumbens CCK function. Behav. Neurosci. 103:831–836; 1989.

39. Vaccarino, F. J.; Schiff, B. B.; Glickman, S. E. Biological view of reinforcement. In: Klein, S. B.; Mowrer, R. R., eds. Contemporary learning theories. Hillsdale, NJ: Lawrence Erlbaum Associates; 1989:111–141.
40. Vaccarino, F. J.; Vaccarino, A. L. Antagonism of cholecystokinin function in the rostral and caudal nucleus accumbens: Differential effects on brain stimulation reward. Neurosci. Lett. 97: 151–156; 1989.
41. Vasar, E.; Stephenson, J. D.; Meldrum, B. S. Changes in motor activity and forebrain [propionyl-^{3}H] propionylated-CCK-8 binding in mice after repeated administration of drugs affecting cholecystokinin receptors. Eur. J. Pharmacol. 202:385–390; 1991.
42. Vickroy, T. W.; Bianchi, B. R.; Kerwin, J. F., Jr.; Kopecka, H.; Nadzan, A. M. Evidence that type A CCK receptors facilitate dopamine efflux in rat brain. Eur. J. Pharmacol. 152:371–372; 1988.
43. Voigt, M.; Wang, R. Y.; Westfall, T. C. Cholecystokinin octapeptides alter the release of endogenous dopamine from the rat nucleus accumbens in vitro. J. Pharmacol. Exp. Ther. 237:147–153; 1986.
44. Voigt, M.; Wang, R. Y.; Westfall, T. C. The effects of cholecystokinin on the in vivo release of newly synthesized [^{3}H]dopamine from the nucleus accumbens of the rat. J. Neurosci. 5:2744–2749; 1985.
45. Weiss, F.; Ettenberg, A.; Koob, G. F. CCK-8 injected into the nucleus accumbens attenuates the supersensitive locomotor response to apomorphine in 6-OHDA and chronic-neuroleptic treated rats. Psychopharmacology (Berlin) 99:409–415; 1989.
46. Weiss, F.; Tanzer, D. J.; Ettenberg, A. Opposite actions of CCK-8 on amphetamine-induced hyperlocomotion and stereotypy following intracerebroventricular and intra-accumbens injections in rats. Pharmacol. Biochem. Behav. 30:309–317; 1988.
47. Zetler, G. Neuropharmacological profile of cholecystokinin-like peptides. In: Vanderhaegen, J. J.; Crawley, J. N., eds. Neuronal cholecystokinin. New York: Academic Press; 1985:448–469.