DEUPREE, DAVID LEE

EFFECTS OF CHOLECYSTOKININ AND BOMBESIN UPON THE HIPPOCAMPAL ELECTROENCEPHALOGRAPH

THE UNIVERSITY OF ARIZONA M.A. 1984

EFFECTS OF CHOLECYSTOKININ AND BOMBESIN UPON THE HIPPOCAMPAL ELECTROENCEPHALOGRAPH

by

David Lee Deupree

A Thesis Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF ARTS

In the Graduate College

THE UNIVERSITY OF ARIZONA

1 9 8 4

STATEMENT BY AUTHOR

This thesis has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: David Kenyon

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

S. Hsiao — February 3, 1984

S. HSIAO — Date

DEDICATION

This thesis is dedicated to Hilsa Ayonayon. Without the constant emotional support provided by Hilsa, completion of this project would not have been possible.

ACKNOWLEDGMENTS

The author wishes to offer special thanks to Dr. Sigmund Hsiao for assistance, guidance, and support throughout this project. Thanks also go to Dr. Mary Wetzel and Dr. Robert Lansing for their support and comments on both the design and writing of this project.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

ABSTRACT

Cholecystokinin (CCK) and bombesin (BBS) are gastrointestinal hormones known to reduce food intake in rats. Both hormones have been found widely distributed in rat brains, with receptor sites for both being located within the central nervous system (CNS) of rats. Both hormones have been found to produce an excitatory effect on hippocampal pyramidal cells using a brainslice preparation. The purpose of the present study was to assess the effects of intraperitoneal (i.p.) injections of CCK and BBS upon hippocampal rhythmic slow activity (RSA) in the anesthetized rat. The results showed a significant decrease in the number of RSA waves counted after the CCK injections, but not after either BBS or saline injections. These results may have implications for explaining the behavioral effects produced by CCK treatment (reductions in food intake, social interactions, and explorative behaviors), as hippocampal RSA has been correlated with the level of an animal's responsiveness to stimuli.

INTRODUCTION

Cholecystokinin (CCK) and bombesin (BBS) are both gastrointestinal hormones known to reduce food intake in rats following intraperitoneal (i.p.) injections (Gibbs, Fauser, Rowe, Rolls, Rolls and Madison, 1979; Gibbs, Young, and Smith, 1973; Hsiao and Deupree, 1983). Both hormones have also been found widely distributed within rat brains (Brown, Allen, Villareal, Rivier, and Vale, 1978; Innis, Correa, Uhl, Schneider, and Snyder, 1979; Pert, Moody, Pert, DeWald, and Rivier, 1980; Saito, Sankaran, Goldfine, and Williams, 1980), and are suspected to be neurotransmitters. Innis, et al. (1979) found CCK-like immunoreactivity throughout rat brains after injecting radioactively labeled CCK antibodies into rats. Highest concentrations of this CCK-like immunoreactivity were found in the dorsal raphe nucleus and periaqueductal gray brainstem regions, with lesser concentrations found in the dorsomedial hypothalamic nucleus, pyriform cortex, amygdala, and the pyramidal cell layer of the hippocampus. Satio, et al. (1980) found specific CCK binding sites within the rat brain. Highest concentration of these binding sites were located in the cerebral cortex, with sites also found within the caudate

nucleus, hippocampus, hypothalamus, and brainstem areas. Brown, et al. (1978) found BBS-like immunoreactivity in various regions of the rat central nervous system (CNS), with highest concentration found in the hypothalamus. Other brain regions found to have BBS-like immunoreactivity were the pons-medulla area, thalamus, cerebral cortex, and hippocampus. Pert, et al. (1980) found BBS receptor sites in rat brains, with the highest concentration of these sites located in limbic-forebrain regions (hippocampus, amygdala, and caudate-putamen), and receptor sites also found in the hypothalamus and periaqueductal gray.

The studies cited above which found CCK and BBS receptor sites and immunoreactivity within the CNS may be used as evidence to demonstrate the existence of CCK-like and BBS-like substances within the rat brain. However, the existence of a substance within the CNS does not indicate its function. Therefore direct measurements have been made of gross electrical brain activity (electrical activity recorded from large populations of cells, using macroelectrodes) after CCK and BBS application. Tartara, Bo, and Savoldi (1982) found that intraventricular infusion of BBS and caerulein (a structural analog of CCK) affected the number of cortical "sleep" spindles recorded in rabbits. In general, the number of these cortical spindles

decreased during the infusion period, for both BBS and caerulein infusions. During the initial infusion period of BBS the number of spindles increased, however as the infusion progressed they dropped below baseline levels. No behavioral changes were noted as a result of either BBS or caerulein infusion. Intraperitoneal injections of CCK have been found to affect averaged auditory evoked potentials recorded from various subcortical CNS regions in rats (Dafny, Jacob, and Jacobson, 1975; Schanzer, Jacobson, and Dafny, 1978). These results are difficult to interpret because the effect of CCK upon the evoked potential within a particular brain site could vary across time. For example, the amplitude of the evoked potential recorded from the ventromedial hypothalamus was found to increase directly under the CCK injection, but later the amplitude was found to markedly decrease. Intravenous infusion of CCK has also been found to affect cortical auditory averaged evoked potentials in humans, as well as the cortical electroencephalogram (EEG) (Stacher, Bauer, and Steinringer, 1979; Stacher, Steinringer, Schmierer, Schneidar, and Winklehner, 1982). Here again the interpretation of the results is difficult because the changes found in the cortical EEG patterns after CCK treatment were not clear cut and in some cases did not reach statistical

significance. In general an increase in cortical slow wave activity (theta and slower alpha activity), as well as an amplitude increase of the evoked potential were found after the CCK treatment. However, increases in the faster cortical activity (beta activity) were also found after the CCK treatment, while the faster alpha activity was found to decrease.

The effects of CCK and BBS application upon fairly discrete cellular populations within the rat CNS have been investigated also. Using electrical iontophoretic injection, Phillis and Kirkpatrick (1980) found that CCK applied near corticospinal neurons resulted in an increase in firing rate, over preapplication baseline rates, of some of these cells (22%). Neurons were identified as cortocospinal based upon action potential latencies following antidromic stimulation of the pyramidal tract. A neuron was considered a cortocospinal neuron if the invading action potential consistently occurred within 5 ms, and if it followed stimulation frequencies of 100/sec or higher. In neurons that could not be identified as corticospinal, 28% were found to increase firing rate following local CCK application. At no time did local CCK application result in a decrease in firing rate, in either identified or unidentified neurons. Skirboll, Grace,

Hommer, Rehfeld, Goldstein, Hokfelt, and Bunney (1981) found that local application of CCK (electrical iontophoretic injection) resulted in increases in firing rates of neurons located in the substantia nigra. Again, no decreases in firing rates were observed. Dood and Kelly (1981), using a brain slice preparation, found icreases in firing rates of hippocampal pyramidial cells during local application (pressure iontophoretic injections) of both CCK and BBS. Using the current injection method Dood and Kelly were able to measure membrane input resistance of the cells. They found that CCK application had the effect of decreasing the input resistance, while BBS did not. Once again, no decreases in cellular firing rates were observed.

The increases in cell firing rates following CCK or BBS application found during the studies cited above may have been mediated through various events, such as the following: (a) CCK and BBS may have been acting as excitatory neurotransmitter-like substances, causing a direct depolarization of the neurons; (b) the hormones may have acted upon presynaptic neurons; (c) the hormones could have been acting within the synapse itself, somehow facilitating the actions of

the normal excitatory neurotransmitter-like substances, causing a direct depolarization of the neurons; (d) the hormones could have been creating passive changes in the membrane resistance; (e) the hormones may have acted upon the metabolic processes of the neurons; and (f) CCK and BBS may have been causing some sort of injury to the cells when applied, with the resulting increase in firing rate being injury potentials. Therefore it can be seen that even though the actions of CCK (and BBS in the Dood and Kelly study) have been consistently reported as excitatory, there are several possible explanations for these observed results.

Despite the lack of clarity regarding the mechanism of actions produced by CCK and BBS upon neurons found during the iontophoretic injection sutdies cited above, there was considerable evidence that application of CCK and BBS produced changes in gross EEG patterns recorded from surface electrodes, or from subcortical sites using macroelectrodes, and changes in unit activity recorded from microelectrodes. In the present study the effects of i.p. injections of CCK and BBS upon the hippocampal EEG of anesthetized rats were investigated. Specifically the effects of these two hormones upon hippocampal rhythmic slow activity (RSA); a high amplitude waveform, ranging in frequency from

approximately 4 - 9 Hz in the rat) were studied. Hippocampal RSA is thought to be generated by the pyramidal cell layers of the hippocampus (Fujita and Sato, 1964) perhaps through recurrent inhibition of basket cells (Andersen, Eccles and Loyning, 1964ab), and thought to be driven by cells located in the medial septal nucleus (Gogolak, Stumpf, Petsche, and Stere, 1968; Apostol and Creutzfldt, 1974).

Hippocampal RSA was chosen for study because it is a prominent waveform of the hippocampal EEG of several mammalian species (Winson, 1972). In addition the hippocampus, and hippocampal RSA, have been correlated with behavioral arousal (Apostol and Creutzfldt, 1974; Green and Arduini, 1954), attention (Bennett, 1975; Lindsley and Wilson, 1975), acquisition of a conditioned response (Berry and Thompson, 1978, 1979; Deupree, Coppock and Willer, 1982), and memory (Destrade, 1982; Landfield, 1977). Although CCK and BBS are both known to reduce food intake (Gibbs, et al., 1973, 1979; Hsiao and Deupree, 1983), it is possible that these actions are not specific to food intake alone. Crawley and coworkers (Crawley, 1983; Crawley, Hays, O'Donohue, Paul, and Goodwin, 1981) have found that CCK treatment will reduce the occurrence of other types of behaviors, such as social interactions and explorative behaviors (arousal and attention).

The major aim of the present study was to determine whether or not CCK and BBS might produce changes in hippocampal RSA, a brain waveform previously linked to arousal and attention (Apostol and Creutzfldt, 1974; Bennett, 1975; Green and Arduini, 1954; Lindsley and Wilson, 1975). It has already been demonstrated that both CCK and BBS will affect hippocampal pyramidal cell activity in the brain slice preparation (Dood and Kelly, 1981). The rationale for the present study was to extend the observations of the effects of CCK and BBS upon larger hippocampal cell populations by measuring hippocampal RSA, a common method for measuring large cellular population activity within the hippocampus. It was also thought that CCK and BBS might differ in the effects they produced upon the hippocampal EEG, because physiological and behavioral differences have been found between the actions produced by CCK and BBS treatment (see Stein and Woods, 1981 for a review).

METHOD

Subjects were 25 male Holtzman rats (3 - 4 months old, and weighing 350 - 480 gms). All were maintained on ad lib food and water. Each rat was anesthetized with a combination of Nembutal (50 mg/Kg i.p.) and Innovar (.5 mg/Kg i.m.). A stainless steel electrode (.00 insect pin coated with epoxy, with a .2 mm tip exposure) was guided into the region of the left dorsal hippocampus (AP + 3.00 mm, ML 2.0 mm, DV -3.0 from cortical surface; using Pellegrino, Pellegrino, and Cushman, 1979). A skull screw was attached to bone overlying the frontal sinus and served as the reference electrode. The rat was grounded to the stereotaxic instrument. Once the placement was completed, 20 - 30 minutes were allowed to pass before data collection began, since the EEG was found to be unstable during the first few minutes after the electrode reached its final position. The raw hippocampal EEG was amplified and recorded on a Grass 7 polygraph, with half-amp settings for bandpass at 3 - 15 Hz. From the polygraph the EEG was fed into a Kronkite 3700 filter set at 4 - 9 Hz (half-amp). The EEG from the filter was also fed into a Simpson 2725 electronic counter whose

threshold was set to detect only the larger amplitude EEG waves. Because of the filtering it was felt that only RSA waves would reach large enough amplitude to exceed the counters threshold. As seen in Figure 1, the counter was activated only when the amplitude of a wave was sufficient to cross the threshold. Polygraph recordings were used to set the counters threshold manually for each rat before data collection began, after the EEG had stabilized. A small sample of the hippocampal EEG (one or two seconds) from the polygraph readout was compared to the count registered on the counters display. The sensitivity of the counter was adjusted by visual inspection until it was found to count only the higher amplitude EEG waves. A 30 second count of RSA waves was collected every minute throughout the test period of 40 minutes.

Ten minutes of baseline RSA counts were collected, and then each rat was given an i.p. injection of one of four treatments: 2 mcg/Kg CCK, 4 mcg/Kg CCK, 12 mcg/Kg BBS, or 9.0% saline. Postinjection RSA counts were made for 30 minutes.

After completion of data collection, a small lesion was produced by passing a 1 mA current (Grass CCU1) for three seconds through the electrode to mark the placement site. The rat was then sacrificed with carbon

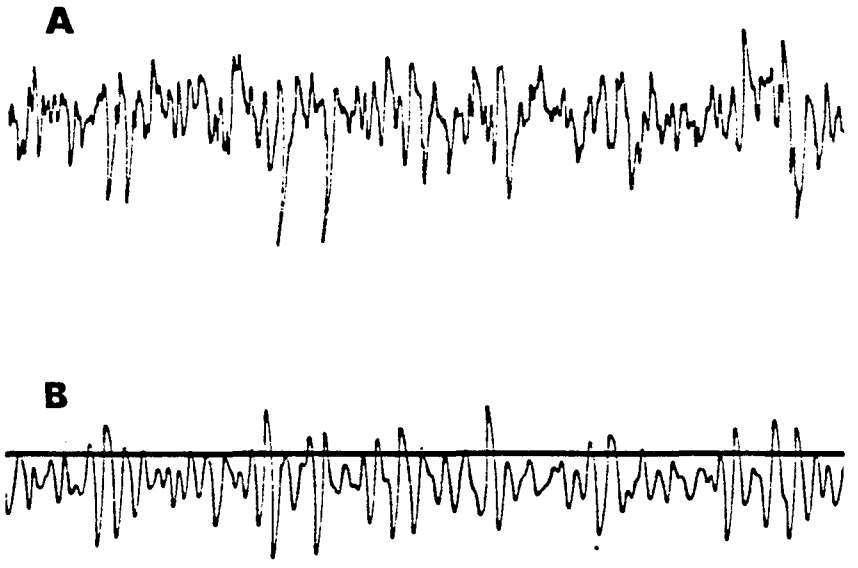

Figure 1. Representative sample of hippocampal EEG as recorded during the study.

A) Raw EEG, filtered at 3 - 15 Hz, directly from the polygraph amps.

B) The same EEG as in A after being fed through the 4 - 9 Hz bandpass filter. Line across B indicates the counter threshold as set by the experimenter using visual inspection of the recordings before data collection began. Any wave whose amplitude crossed the threshold would be counted by the counter.

dioxide and perfused with 0.9% NaCl, followed by a 10% Formalin solution. The brain was extracted and placed in the Formalin solution, where it remained for at least 48 hours. Frozen slices, 40 microns thick, were made from the tissue which surrounded the electrode track and lesion. Placement sites were marked on copies of the atlas plate used for coordinates. Five rats were found to have placements sites outside the dorsal hippocampus, and the data from these five rats were discarded. The final total number of subjects within each of the four treatment groups was five rats.

RESULTS

The RSA counts for each rat were grouped into four successive time blocks (one preinjection, and three postinjection), each composed of the RSA counts of ten consecutive minutes. TAble 1 (a - d) contains the total RSA counts for each rat at all four time blocks. Also included were the means and standard deviations for each time block. These data were analyzed for within groups differences using the Friedman nonparametric test for repeated ranks, with post-hoc testing performed using Nemenyi's specific-comparison test, which adjusts for alpha slippage over several testings (Linton and Gallo, 1975).

Table 1a contains the total RSA counts of the saline treated rats at each time block. No significant overall differences were found between the time blocks, $X^2(3) = 3.96$, n.s.

Table 1b contains the total RSA counts of the BBS 12 mcg/Kg treated rats at each time block. Analysis of these data found an overall difference between the time blocks, $X^2(3) = 8.04$, p .05. However once alpha slippage was accounted for, post-hoc testing revealed no significant differences between any of the time blocks.

Table 1a. Total RSA Counts at Each Time Block.

Saline Rats				
Rat	Baseline	Post I	Post II	Post III
1	1016	1042	1056	1057
2	1041	923	871	791
3	1038	876	943	860
4	1417	1338	1147	1303
5	1450	1372	1316	1335
Mean	1192.4	1110.2	1066.6	1069.2
S.D.	220.6	231.8	174.9	248.3

Table 1b. Total RSA Counts at Each Time Block.

BBS Rats 12 mcg/Kg				
Rat	Baseline	Post I	Post II	Post III
1	1137	1095	1114	1175
2	1178	1158	1157	991
3	1354	1228	1157	1180
4	1148	982	943	743
5	1204	1059	1025	1013
Mean	1202.4	1104.4	1079.2	1020.4
S.D.	87.8	93.9	93.3	178.4

Table 1c. Total RSA Counts at Each Time Block.

CCK Rats 2 mcg/Kg				
Rat	Baseline	Post I	Post II	Post III
1	1216	1053	1035	914
2	1072	889	753	667
3	1079	735	885	752
4	1182	1087	993	951
5	1261	1246	1128	1136
Mean	1162.0	1002.0	958.8	884.0
S.D.	83.8	195.8	144.4	182.6

Table 1d. Total RSA Counts at Each Time Block.

CCK Rats 4 mcg/Kg				
Rat	Baseline	Post I	Post II	Post III
1	1165	1078	960	942
2	1255	1067	1074	937
3	1495	1436	1287	1305
4	1231	1061	1030	971
5	1155	1063	1062	992
Mean	1260.2	1141.0	1083.2	1029.4
S.D.	138.0	165.0	122.5	155.7

Table 1c contains the total RSA counts for the CCK 2 mcg/Kg treated rats at each time block. An overall difference was found between the time blocks, $X^2(3) = 11.16$, $p < .05$, with the third postinjection time block ranks (minutes 21 - 30 postinjection) found to be lower than the preinjection time block ranks ($p < .05$).

Table 1d contains the total RSA counts of the CCK 4 mcg/Kg treated rats at each time block. An overall difference was found between the time blocks, $X^2(3) = 12.84$, $p < .01$, with the third postinjection time block ranks found to be lower than the preinjection time block ranks ($P < .05$).

Between groups differences at each time block were tested for by using the Kruskal-Wallis nonparametric test for between group ranks. No significant differences were found between the various treatment group rankings at any of the four time blocks.

DISCUSSION

This study showed a decrease in the number of hippocampal RSA waves counted following i.p. injections of CCK in the anesthetized rat. This finding was obtained for both dosages of CCK used during the study. Even though the CCK treated rats were found to have significantly lower hippocampal RSA ranks during the third post-injection time block, as compared to the preinjection time block, it is noted that this effect was relatively weak. The fact that no between-groups differences were found supports the conclusion that the CCK effect upon the hippocampal EEG was weak; a large reduction in hippocampal RSA counts was not observed. However one cannot equate statistical strength with physiological strength. Reductions were found in hippocampal RSA counts after the CCK injections, whether this effect is physiologically significant is not known. It is difficult at this time to reach a clear conclusion concerning the BBS treatment upon the hippocampal EEG. There was an overall trend in the data of the BBS treated rats, as indicated by the significant value of the Friedman test. However this trend did not

reveal itself with significant differences between any of the time blocks upon post-hoc testing with a conservative test.

The physiological mechanisms and anatomical pathways for the actions produced by the systemic introduction of CCK upon the hippocampal EEG observed during this study are not clear at present. The question of whether or not systemic CCK can produce direct actions upon the brain is unresolved. The fact that the CCK treatment used in this study did affect the hippocampal EEG does not prove that systemic CCK can produce direct central effects. Skirboll, et al. (1981) found that both direct brain application (iontophoretic injection) and systemic application (intravenious injection) of CCK produced similar effects upon rat cortical neurons, although the systemic treatment was less effective in producing the observed increases in firing rates. Their findings lend support to the hypothesis that CCK may produce direct central effects. On the other hand, there is evidence that systemic CCK may influence brain activity through the vagus nerve. Gastric vagotomy has been found to abolish the food reduction effect of CCK in rats (Smith, Jerome, Cushin, Eterno, and Simansky, 1981). In addition CCK receptors have been found in the vagus nerve

(Zarbin, Wamsley, Innis, and Kuhar, 1981). It is entirely possible, of course, that systemic CCK may produce both direct and indirect effects upon the brain.

Even if systemic CCK can affect the brain directly, the site of action within the brain that resulted in the effect upon the hippocampal EEG is still unknown. Two main hypotheses, not mutually exclusive, bear upon this localization question. One hypothesis would be that the CCK effect observed upon the hippocampal EEG was produced at some brain site other than the hippocampus. It is known that the medial septal nucleus has direct anatomical and functional relationships with the dorsal hippocampus (Berger and Thompson, 1977; Dudar, 1975; Lewis and Shute, 1967; Solomon and Gottfried, 1981). The medial septal nucleus is also known to be important for the occurrence of hippocampal RSA (Apostol and Creutzfeldt, 1974; Gaztelu and Buno, 1982). In addition it has been found that electrical stimulation of several reticular formation and hypothalamic sites will affect hippocampal RSA (Lindsley and Wilson, 1975; Pavia, Lopes Da Silva, and Mollevanger, 1976). It is not clear whether the CCK treatment used in the present study affected the hippocampus directly, through this brainstem-hypothalamic-septal pathway, or through some other route entirely.

The other plausible hypothesis concerning a possible direct central action of systemic CCK upon the brain would be that CCK may have a direct influence within the hippocampus itself. This influence may occur on hippocampal receptors, or may somehow act upon hippocampal neurons in some other manner, not specified at present. Dood and Kelly (1981) found local application of CCK and BBS had a direct effect within the hippocampus. The increases firing rates of hippocampal pyramidal cells that were observed may have been produced through indirect actions (even though it is clear that the effect originated within the hippocampus). One way to account for the decreases in RSA observed during the present study would be to interpret the results of Dood and Kelly (1981) to indicate that the increases in pyramidal cell firing rates they observed would result in a more desynchronized hippocampal EEG overall in the intact rat, and therefore less RSA. It is a common hypothesis (see Andersen and Andersson, 1968; and Creutzfeldt, 1969) that the desynchronized EEG which is recorded from large populations of cells may be due to activity of neurons that occurs in a random (desynchronized) manner. Conversely, rhythmical EEG would be a reflection of synchronized activity of cells. Future testing of this particular hypothesis might include recording hippocampal multiple-unit activity

(activity of the small group of cells just adjacent to the microelectrode tip) from the pyramidal cell layer, in addition to gross hippocampal EEG, before and after CCK treatment. To support this hypothesis, the recordings should show an increase in the multiple-unit activity following CCK treatment, as well as a corresponding decrease in RSA. Having both a systemic treatment and a central treatment group would help to clarify the question as to whether or not CCK can produce direct central effects.

The results of the present study may have implications for research investigating the functional significance of CCK treatment. Hippocampal RSA has been linked with arousal (Apostol and Creutzfeldt, 1974; Green and Arduini, 1954), attention (Bennett, 1975; Lindsley and Wilson, 1975), learning (Berry and Thompson, 1978, 1979; Deupree, et al., 1982), and memory (Destrade, 1982; Landfield, 1977). CCK has been found to make rats less responsive to a variety of stimuli (Crawely, 1983; Crawely, et al., 1982), as well as food related stimuli (Gibbs, et al., 1973; Hsiao and Deupree, 1983). The results of the present study were that CCK affected hippocampal RSA, a brain waveform related to an animal's responsiveness to stimuli. To interpret the effects of CCK upon hippocampal RSA that were observed during the present study in terms of behavioral significance would require concomitant behavioral surveys.

The rats used in the present study were anesthetized, so no behavioral changes could be correlated with the observed hippocampal EEG changes. The present study established that the injection of CCK resulted in reductions of hippocampal RSA. Future research would need to verify that this effect upon the hippocampal EEG can be observed in the unanesthetized rat as well. In addition the correlation between behavior changes and hippocampal EEG changes resulting from CCK treatment will need to be established with further research.

REFERENCES

Andersen, P., and Andersson, S. A. Physiological Basis of the Alpha Rhythm. New York: Appleton-Century-Crofts, 1968.

Andersen, P., Eccles, J. C., and Loyning, Y. Location of postsynaptic inhibitory synapes on hippocampal pyramids. Journal of Neurophysiology, 1964a, 27, 592-607.

Andersen, P., Eccles, J. C., and Loyning, Y. Pathway of postsynaptic inhibition in the hippocampus. Journal of Neurophysiology, 1964b, 27, 608-619.

Apostol, G., and Creutzfeldt, O. T. Crosscorrelation between the activity of septal units and hippocampal EEG during arousal. Brain Research, 1974, 67, 65-75.

Bennett, T. L. The electrical activity of the hippocampus and processes of attention. In Isaacson and Pribram (Eds.), The Hippocamus (Vol. 2). New York: Plenum Press, 1975.

Berger, T. W. and Thompson, R. F. Limbic system interactions: Functional division among hippocampal-septal connections. Science, 1977, 197, 587-589.

Berry, S. D., and Thompson, R. F. Prediction of learning rate from the hippocampal EEG. Science, 1978, 200, 1298-1300.

Berry, S. D., and Thompson, R. F. Medial septal lesions retard classical conditioning of the nicitating membrane response in rabbits. Science, 1979, 205, 209-211.

Brown, M., Allen, R., Villareal, J., Rivier, J., and Vale, W. Bombesin-like activity; Radioimmuno logic assessment in biological tissues. Life Sciences, 1978, 23, 2721-2728.

Crawley, J. N. Cholecystokinin accelerates the rate of habituation to a novel environment. Pharmacology Biochemistry, and Behavior, 1983 (in press).

Crawley, J. N., Hays, S. E., O'Donohue, T. L., Paul, S. M., and Goodwin, F. K. Neuropeptide modulation of social and exploratory behaviors in laboratory rodents. Peptides, 1981, 2(1), 123-129.

Creutzfeldt, O. D. Neuronal mechanisms underlying the EEG. In Jasper, Ward, and Pope (Eds), Basic Mechanisms of the Epilepsies. Boston: Little. Brown and Company, 1969.

Dafny, N., Jacob, R. H., and Jacobson, E. D. Gastro-intestinal hormones and neural interaction within the central nervous system. Separatum Experientia, 1975, 31, 658-659.

Destrade, C. Two types of diencephalically driven RSA (theta) as a means of studying memory formation in mice. Brain Research, 1982, 234, 486-493.

Deupree, D., Coppock, W., and Miller, H. Pertaining septal driving of hippocampal rhythmic slow activity facilitates acquisition of visual discrimination. Journal of Comparative and Physiological Psychology, 1982, 96(4), 557-562.

Dood, J., and Kelly, J. S. The actions of cholecystokinin and related peptides on pyramidal neurons of the mammalian hippocampus. Brain Research, 1981, 205, 337-350.

Dudar, J. D. The effect of septal nuclei stimulation on the release of acetylcholine from the rabbit hippocampus. Brain Research, 1975, 83, 123-133.

Fujita, Y., and Sato, T. Intracellular records from hippocampal pyramidal cells in rabbit during theta rhythm activity. Journal of Neurophysiology, 1964, 27, 1011-1025.

Gatzelu, J. M., and Buno, W. Septo-hippocampal relationships during EEG theta rhythm. Electroencaphalography and Clinical Neurophysiology, 1982, 54, 375-387.

Gibbs, J., Fauser, D. J., Rowe, E. A., Rolls, B. J., Rolls, E. T., and Maddison, S. P. Bombesin supresses feeding in rats. Nature, 1979, 282, 208-210.

Gibbs, J. R., Young, C., and Smith, C. P. Cholecystokinin decreases food intake in rats. Journal of Comparative and Physiological Psychology, 1973, 84, 488-495.

Gogolak, G., Stumpf, C., Petsche, H., and Stere, J. The firing pattern of septal neurons and the form of the hippocampal theta wave. Brain Research, 1968, 7, 201-207.

Green, J.D., and Arduini, A. A. Hippocampal electrical activity in arousal. Journal of Neurophysiology, 1954, 17, 553-557.

Hsiao, S., and Deupree, D. Cholecystokinin and bombesin effects on rewarded and nonrewarded operants. Peptides, 1983, (in press).

Innis, R. B., Correa, F. M. A., Uhl, G. R., Schneider, B., and Snyder, S. H. Cholecystokinin octapeptide-like immunoreactivity: Histological localization in the rat brain. Proc. Natn. Acad. Sci. U.S.A., 1979, 76, 521-525.

Landfield, P. W. Different effects of porttrial driving or blocking of the theta rhythm on avoidance learning in rats. Physiology and Behavior, 1977, 18, 439-445.

Lewis, P. R., and Shute, C. C. D. The cholinergic limbic system: Projections to hippocampal formation, medial cortex, nuclei of the ascending cholingeric reticular system, and the subfornical organ and supraoptic crest. Brain Research, 1967, 90, 521-539.

Lindsley, D. B., and Wilson, C. L. Brainstem-hypothalamic systems influencing hippocampal activity and behavior. In Isaacson and Pribram (Eds.), The Hippocampus, (Vol. 2). New York: Plenum Press; 1975.

Linton, M., and Gallo, P. S. The Practical Statistician: Simplified Handbook of Statistics. Monterey, CA., Brooks/Cole, 1975.

Pavia, T., Lopes Da Silva, F. H., and Mollevanger, W. Modulating systems of hippocampal EEG. Electroencaphalography and Clinical Neurophysiology, 1976, 40, 470-480.

Pellegrino, L. J., Pellegrino, A. S., and Cushman, A. J. A Stereotaxic Atlas of the Rat Brain. New York: Plenum Press, 1979.

Pert, A., Moody, T. W., Pert, C. B., DeWald, L. A., and Rivier, J. Bombesin: Receptor distribution in brain and effects on nocioception and locomotor activity. Brain Research, 1980, 193, 209-220.

Phillis, J. W., and Kirkpatrick, J. R. The actions of motilin, lutenizing hormone releasing hormone, cholecystokinin, somatosatin, vasoactive intestinal peptide, and other peptides on rat cerebral cortical neurons. Canadian Journal of Pharmacology, 1980, 58, 612-623.

Saito, A., Sankaran, H., Goldfine, I. D., and Williams, J. A. Cholecystokinin receptors in the brain: Characterization and distribution. Science, 1980, 208, 1155-1156.

Schanzer, M. C., Jacobson, E. D., and Dafny, N. Endocrine control of appetite: Gastrointestinal hormone effects on CNS appetitive structures. Neuroendocrinology, 1978, 25, 329-342.

Skirboll, L. R., Grace, A. A., Hommer, D. W., Rehfeld, J., Goldstein, M., Hokfelt, T., and Bunney, B. S. Peptide-monoamine coexistence: Studies of the actions of cholecystokinin-like peptide on the electrical activity of midbrain dopamine neurons. Neuroscience, 1981, 6, 2111-2124.

Solomon, P. R., and Gottfried, K. E. The septohippocampal cholinergic system and classical conditioning of the rabbit's nicitating membrane response. Journal of Comparative and Physiological Psychology, 1981, 95, 322-330.

Smith, G. P., Jerome, C., Cushin, B. J., Eterno, R., and Simansky, K. J. Abdominal vagotomy blocks the satiety of cholecystokinin in the rat. Science, 1981, 213, 1036-1037.

Stacher, G., Bauer, H., and Steinringer, H. Cholecystokinin decreases appetite and activation evoked by stimuli arising from the preparation of a meal in man. Physiology and Behavior, 1979, 23, 325-331.

Stacher, G., Steinringer, H., Schmierer, G., Schneider, C., and Winklehner, S. Cholecystokinin octapeptide decreases intake of solid food in man. Peptides, 1982, 1, 133-136.

Stein, L. J., and Woods, S. C. Cholecystokinin and bombesin act independently to decrease food intake in the rat. Peptides, 1981, 2, 431-436.

Tartara, A., Bo, P., and Savoldi, F. Neuropeptides and cerebral electric activity in rabbits. Peptides, 1982, 1, 125-127.

Winson, J. Interspecies differences in the occurrence of theta. Behavioral Biology, 1972, 7, 479-488.

Zarbin, M. A., Wamsley, J. K., Innis, R. B., and Kuhar, M. J. Cholecystokinin receptors: Presence and axonal flow in the rat vargus nerve. Life Sciences, 1981, 29, 697-705.