Cholecystokinin and GABA interaction in the dorsal hippocampus of rats in the elevated plus-maze test of anxiety

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Abstract

In the present study, we have investigated the effects and interaction of CCK and GABAergic systems in the dorsal hippocampus of rats using the elevated plus-maze test of anxiety. Bilateral injection of different doses of CCK8s (0.01, 0.05 and 0.1 µg/rat) into the dorsal hippocampus (intra-CA1) decreased percentage of open arm time (%OAT) and open arm entries (%OAE) that are representative of anxiogenic-like behavior. The bilateral injection of three doses of LY225910, a selective CCK2 receptor antagonist (0.01, 0.1 and 0.5 µg/rat) produced significant anxiolytic behavior. Although muscimol (GABA_A) (0.1, 0.5 and 1 µg/rat, intra-CA1) produced dose dependent increase in %OAT and a slight increase in %OAE, bicuculline (GABA_A/C0), (1, 2 and 4 µg/rat, intra-CA1) failed to change the anxiety profile. Both muscimol (0.1 µg/rat) and bicuculline (1 µg/rat), when co-administered with LY225910, reversed the effect of latter drug on anxiety but when co-administered with CCK8s (0.05 µg/rat) showed no effect on anxiety profile. In conclusion, it seems that both CCK and GABAergic systems not only play a part in the modulation of anxiety in the dorsal hippocampus of rats but also have demonstrated a complex interaction as well.

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Keywords: Cholecystokinin; GABA; Anxiety; Dorsal hippocampus; Rat

1. Introduction

Cholecystokinin (CCK) is a gastrin-like peptide originally discovered in the gut and later on identified in the brain [1]. This neuropeptide, widely distributed throughout the brain, is acting as a neurotransmitter [2]. Two CCK receptor subtypes have been recognized (CCK1 and CCK2) [3,4]. CCK1 receptors are mainly located in the periphery and are known to mediate feeding [5]. On the other hand, CCK2 receptors are located in the CNS and have been mainly implicated in the control of exploratory behavior and development of anxiety [6,7]. Pharmacological data demonstrated that CCK peptides and their receptors play an important role in the neurobiological mechanisms of stress and anxiety-related behaviors [8]. The involvement of central CCK2 receptors in anxiogenesis [9–11] and mediating panic attacks [12] are controversial [13,14]. This applies to the CCK2 receptor antagonists as well. Some reports have demonstrated the anxiolytic effects of CCK2 receptor antagonists [6,15], while others failed to demonstrate these effects [13,16]. In behavioral studies, CCK showed an interaction with other neurotransmitters such as histamine in feeding [5], 5-HT in feeding [17] and anxiety [18] as well as GABA in analgesia [19] and convulsion [20]. In the CNS, CCK is co-localized in neurons with many neurotransmitters or modulators such as dopamine, oxytocin, β-endorphine, adrenocorticotropic, neurotensin and GABA [2,21].

GABA is the main central inhibitory neurotransmitter, which is found in all areas of the human brain. GABA receptors in the brain have been classified as GABA_A, GABA_B and GABA_C [22]. The involvement of GABA...
receptors in the modulation of anxiety has been the subject of extensive studies. Activation of GABA_A receptors, but not GABA_B receptors, demonstrated anxiolytic effects [23–25]. The brain regions where CCK_2 receptors exert their anxiogenic activities are still undefined [26], and studies assessing the effect of intra-hippocampal injection of CCK fragments on anxiety are lacking. Several central sites have been suggested to play a part in the modulation of fear or anxiety. Among the CNS sites, hippocampus is suggested to have an important role [27,28]. Because of high density of both CCK receptors and CCK-like immunoreactivity in the hippocampus and the extensive co-localization of CCK and GABA in this CNS region, the effects of CCK and its interaction with GABA-containing neurons in this area of the brain have been explored [2,4]. One of the animal models for the study of anxiolytic or anxiogenic drugs is elevated plus-maze (EPM) [29]. Based on these findings the aim of the present study was to investigate the effects of CCK_{8s} and CCK_2 receptor antagonist on anxiety and their possible interaction with GABA in the CA1 region of the hippocampus using elevated plus-maze in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats from Pasteur Institute (Iran), weighing 180–230 g at the time of surgery, were used. Animals were housed four per cage, in a room with a 12:12 h light/dark cycle (lights on 07:00 hours) and controlled temperature (23 ± 1 °C). Animals had access to food and water ad libitum and were allowed to adapt to the laboratory conditions for at least 1 week before surgery. Rats were handled about 3 min each day prior to behavioral testing. All experiments were performed between 9:00 and 13:00 hours and each rat was tested only once. Seven animals were used in each group of experiments.

2.2. Stereotaxic surgery and microinjections

Rats were anesthetized intraperitoneally with ketamine hydrochloride (50 mg/kg) and xylazine (4 mg/kg) and placed in a Kopf stereotaxic instrument. The stainless steel guide cannula (22-gauge) was implanted in the right and left CA1 regions according to Paxinos and Watson [30]. Stereotaxic coordinates for the CA1 regions of the dorsal hippocampus were: −2.6 to −2.9 mm (depending on body weight) posterior to bregma, ±1.6–1.8 mm lateral to the midline and −2.5 to −2.8 mm ventral of the dorsal surface of the skull. The cannula was fixed to the skull with acrylic dental cement. The animals were allowed 5 days before the test to recover from surgery.

The left and right CA1 were infused by means of an internal cannula (27-gauge), terminating 1 mm below the tip of the guides, connected by polyethylene tubing to a 1-μl Hamilton syringe. On each side 0.5 μl solution was injected (1 μl/rat) over a 60 s period. The inner cannula was left in place for an additional 60 s to allow diffusion of the solution and to reduce the possibility of reflux. Intra-CA1 injections were made 5 min before testing.

2.3. Elevated plus-maze

The method is basically the same as described by Pellow and File [29]. The elevated plus-maze was a wooden, cross-shaped maze, consisting of four arms arranged in the shape of a plus sign. Two of the arms have no side or end walls (open arms; 50 × 10 cm). The other two arms have side walls and end walls, but are open on the top (closed arms; 50 × 10 × 40 cm). Where the four arms intersect, there is a square platform of 10 × 10 cm. The maze was elevated to a height of 50 cm. In order to elevate total arm entries on the maze, rats were placed in a wooden test arena (50 × 50 × 35 cm) for 5 min prior to maze testing. Five days after implantation, the effects of bilateral intra-hippocampal injection of drugs were tested in the elevated plus-maze. The animals were individually placed in the center of the maze facing an open arm and allowed 5 min of free exploration. All sessions were videotaped and the number of entries into the open arms, the number of entries into the closed arms, and the total time spent in the open arms and total time spent in the closed arms were measured. Entry was defined as all four paws in the arms. The percentage of open arm entries and open arm time as the standard anxiety indices [28] were calculated as follows: (a) %OAE (the ratio of entries into open arms to total entries × 100); (b) %OAT (the ratio of times spent in the open arms to total times spent in any arms × 100). Total arm entries were considered as the index of locomotor activity [29].

2.4. Drugs

The drugs used in the present study were (+)-bicuculline and muscimol hydrobromide (Sigma Chemical Co., USA), LY225910 (2-[2-Bromo-1H-indol-3-yl]ethyl]-3-[3-(1-methyl-ylethoxy)phenyl]-4-(3H)-quinazoline) and CCK_{8s} (Asp-Tyr(SO_{3H})-Met-Gly-Trp-Met-Asp-Phe-NH_{2}) (Tocris Cookson, UK). Muscimol was dissolved in the sterile 0.9% saline; bicuculline was dissolved in one drop of glacial acetic acid and made up to volume of 5 ml with sterile 0.9% saline. CCK_{8s} was dissolved in 0.05 M sodium bicarbonate solution. LY225910 was dissolved in DMSO (up to 10% v/v) and sterile 0.9% saline.

2.5. Drug treatments

2.5.1. Experiment 1: effects of CCK agonist on anxiety

Four groups of rats were used in this experiment. The first group received vehicle (1 μl/rat, intra-CA1). Other groups received 3 different doses of CCK_{8s} (0.01, 0.05 and 0.1 μg/rat, intra-CA1).
2.5.2. Experiment 2: effects of GABA_A agonist alone or with CCK agonist on anxiety

Four groups of rats received saline (1 μl/rat, intra-CA1). Three min later, the first group received the same dose of saline. The other groups received 3 different doses of muscimol (0.1, 0.5 and 1 μg/rat, intra-CA1). Four other groups received an intra-CA1 injection of CCK_8s (0.05 μg/rat, intra-CA1) 3 min before injection of either saline (1 μl/rat, intra-CA1) or muscimol (0.1, 0.5 and 1 μg/rat, intra-CA1).

2.5.3. Experiment 3: effects of GABA_A antagonist alone or with CCK agonist on anxiety

Four groups of rats received saline (1 μl/rat, intra-CA1). Three min later, the first group received vehicle (1 μl/rat, intra-CA1) and other groups received 3 different doses of bicuculline (1, 2 and 4 μg/rat, intra-CA1). Four other groups received an intra-CA1 injection of CCK_8s (0.05 μg/rat, intra-CA1) 3 min before injection of either vehicle (1 μl/rat, intra-CA1) or bicuculline (1, 2 and 4 μg/rat, intra-CA1).

2.5.4. Experiment 4: effects of CCK agonist alone, with GABA_A agonist or GABA_A antagonist on anxiety

Four groups of rats received saline (1 μl/rat, intra-CA1). Three min later, the first group received vehicle (1 μl/rat, intra-CA1) and other groups received 3 different doses of LY225910 (0.01, 0.1 and 0.5 μg/rat, intra-CA1). Four other groups of rats received an intra-CA1 injection of bicuculline (1 μg/rat, intra-CA1) 3 min before injection of vehicle (1 μl/rat, intra-CA1) or LY225910 (0.01, 0.1 and 0.5 μg/rat, intra-CA1). Another four groups of rats received an intra-CA1 injection of muscimol (0.1 μg/rat, intra-CA1) 3 min before injection of vehicle (1 μl/rat, intra-CA1) or LY225910 (0.01, 0.1 and 0.5 μg/rat, intra-CA1).

2.6. Statistical analysis

Since data displayed normality of distribution and homogeneity of variance, one-way ANOVA was used for comparison between the effects of different doses of drugs with vehicle. Two-way ANOVA was used for evaluation of interactions between drugs. Following a significant F-value, post hoc analysis (least significant difference, LSD) was performed for assessing specific group comparisons. Differences with P<0.05 between experimental groups at each point were considered statistically significant.

3. Results

3.1. Verification of cannula placements

Fig. 1 illustrates the approximate point of the drug injections in the CA1. The histological results were plotted on representative sections taken from the rat brain atlas of Paxinos and Watson [30]. After completion of the experimental sessions, rats received a 0.5 μl/side of methylene blue. Approximately 5–10 min after the injection, the animals were decapitated and their brains were removed, blocked and cut coronally in 40-μm sections through both cannula placements. Data from the rats with injection sites located outside the CA1 were not used in the analysis.

3.2. Effects of CCK agonist on anxiety

Fig. 2 shows the effect of intra-CA1 injection of CCK_8s, in the elevated plus-maze in rats. One-way ANOVA revealed that CCK_8s decreased %OAT [F (3,24)=4.23, P<0.05] at the doses of 0.05 and 0.1 μg/rat and %OAE [F (3,24)=4.37, P<0.05] at the doses of 0.01, 0.05 and 0.1 μg/rat indicating the induction of anxiogenic response by CCK_8s. No change in the locomotor activity was observed [F (3,24)=1.11, P>0.05]. However, the result obtained with %OAT tends to be bell shaped.

3.3. Effects of GABA_A agonist alone or with CCK agonist on anxiety

Effects of intra-CA1 injections of the GABA_A receptor agonist, muscimol and CCK_8s (0.05 μg/rat) on the response induced by muscimol are shown in Fig. 3. Two-way ANOVA analysis indicated that the combination of muscimol (Factor A) with CCK_8s (Factor B) showed no interactions between the effects of muscimol and CCK_8s on %OAT [Factor A; F (3,48)=8.23, P<0.001, Factor B; F (1,48)=3.35, P<0.05, Factor (A×B); F (3,48)=1.34, P>0.05], %OAE [Factor A; F (3,48)=2.83, P<0.05, Factor...
B; $F(1,48) = 4.73, P<0.05$, Factor (A × B); $F(3,48) = 0.83, P>0.05$] and locomotor activity [Factor A; $F(3,48) = 0.07, P>0.05$, Factor B; $F(1,48) = 0.26, P>0.05$, Factor (A × B); $F(3,48) = 1.65, P>0.05$]. Post hoc analysis indicated that muscimol significantly increased %OAT at the doses of 0.5 and 1 µg/rat and %OAE at the dose of 1 µg/rat but not locomotion. The above result is suggestive of an anxiolytic effect of muscimol.

### 3.4. Effects of GABA$_A$ antagonist alone or with CCK agonist on anxiety

Fig. 4 shows the effects of intra-CA1 injections of the GABA$_A$ receptor antagonist, bicuculline (1, 2 and 4 µg/rat) and CCK$_{8s}$ (0.05 µg/rat) on the response induced by bicuculline. Two-way ANOVA analysis showed no inter-

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**Fig. 2.** Anxiogenic effect of bilateral intra-hippocampal CA1 injection of CCK$_{8s}$ in the elevated plus-maze. Rats were treated with either vehicle (1 µl/rat) or with CCK$_{8s}$ (0.01, 0.05 and 0.1 µg/rat). Each bar is mean ± S.E.M. %Open Arm Time (A), %Open Arm Entries (B) or locomotor activity (C). $N=7$. *$P<0.05$, **$P<0.01$, when compared to the vehicle treated rats.

**Fig. 3.** The effect of bilateral intra-hippocampal CA1 injection of muscimol in the presence or absence of CCK$_{8s}$ (intra-CA1) in the elevated plus-maze. Rats were injected saline (1 µl/rat, intra-CA1) or muscimol (0.1, 0.5 and 1 µg/rat, intra-CA1) 3 min after injection of either saline (1 µl/rat, intra-CA1) or CCK$_{8s}$ (0.05 µg/rat, intra-CA1). Each bar is mean ± S.E.M. %Open Arm Time (A), %Open Arm Entries (B) or locomotor activity (C). $N=7$. *$P<0.05$, **$P<0.01$, ***$P<0.001$, when compared to the saline treated rats.

**Fig. 4.** Effects of intra-CA1 injections of the GABA$_A$ receptor antagonist, bicuculline (1, 2 and 4 µg/rat) and CCK$_{8s}$ (0.05 µg/rat) on the response induced by bicuculline. Two-way ANOVA analysis showed no inter-
actions between the effects of bicuculline (Factor A) and CCK\textsubscript{8s} (Factor B) on %OAT [Factor A; $F(3,48) = 0.25$, $P > 0.05$, Factor B; $F(1,48) = 2.91$, $P < 0.05$, Factor (A x B); $F(3,48) = 1.41$, $P > 0.05$], %OAE [Factor A; $F(3,48) = 0.19$, $P > 0.05$, Factor B; $F(1,48) = 0.15$, $P > 0.05$, Factor (A x B); $F(3,48) = 0.06$, $P > 0.05$] and locomotor activity [Factor A; $F(3,48) = 1.15$, $P > 0.05$, Factor B; $F(1,48) = 1.23$, $P > 0.05$, Factor (A x B); $F(3,48) = 1.33$, $P > 0.05$], indicating no effect for bicuculline and no interaction between bicuculline and CCK\textsubscript{8s} on anxiety-related behaviors.

3.5. Effects of CCK\textsubscript{2} antagonist without or with GABA\textsubscript{A} agonist or GABA\textsubscript{A} antagonist on anxiety

Fig. 5 shows the effects of intra-CA1 injections of CCK\textsubscript{2} selective antagonist, LY225910 (0.01, 0.1 and 0.5 \(\mu\text{g/rat}, \text{intra-CA1}\)) in the presence or absence of either bicuculline or muscimol. Two-way ANOVA showed an interaction between the influence of LY225910 (Factor A) and those induced by bicuculline (Factor B) on %OAT [Factor A; $F(3,48) = 4.30$,...
P < 0.01, Factor B; F (1,48) = 1.96, P > 0.05, Factor (A × B); F (3,48) = 2.96, P < 0.05 and on %OAE [Factor A; F (3,48) = 3.24, P < 0.05, Factor B; F (1,48) = 2.21, P > 0.05, Factor (A × B); F (3,48) = 2.85, P < 0.05] but not on locomotor activity [Factor A; F (3,48) = 1.86, P > 0.05, Factor B; F (1,48) = 0.44, P > 0.05, Factor (A × B); F (3,48) = 0.86, P > 0.05]. Post hoc analysis showed that LY225910 increased %OAT and %OAE at the doses of 0.1 and 0.5 μg/rat. The data indicate that LY225910 induced anxiolytic effect which was reduced by bicuculline.

Moreover, two-way ANOVA showed an interaction between the influence of LY225910 (Factor A) and those induced by muscimol (Factor C) on %OAT [Factor A; F (3,48) = 3.36, P < 0.05, Factor C; F (1,48) = 1.71, P > 0.05, Factor (A × C); F (3,48) = 2.91, P < 0.05], but not on %OAE [Factor A; F (3,48) = 3.33, P < 0.05, Factor C; F (1,48) = 1.17, P > 0.05, Factor (A × C); F (3,48) = 1.87, P > 0.05] and on locomotor activity [Factor A; F (3,48) = 1.51, P > 0.05, Factor C; F (1,48) = 2.17, P > 0.05, Factor (A × C); F (3,48) = 0.27, P > 0.05]. The results indicate that muscimol decreased anxiolytic effect of LY225910. Overall the data may show that the anxiolytic effect of LY225910 may be mediated through GABA receptor mechanism(s).

4. Discussion

Hippocampus is an important site in the modulation of fear and anxiety-related behaviors (see Introduction). We have investigated the effects of CCK and its interaction with GABA system on anxiety in the elevated plus-maze.

In the present study, bilateral injection of CCK8s, a non-selective CCK1 and CCK2 receptor agonist into the dorsal hippocampus (intra-CA1) decreased %OAT and %OAE indicating that the drug produced anxiogenic-like behavior without affecting locomotor activity. Effect of CCK8s on %OAT was tended to be bell shaped. The bell shaped dose response has been reported for peptides [31,32]. The results are also consistent with other studies that showed an anxiogenic effect for CCK fragments following systemic [9,10], intracerebroventricular [33] or intradorsal periaqueductal gray [11] administration. Our results may suggest that CCK peptides in the dorsal hippocampus are also involved in the modulation of anxiety-related behaviors. Other investigators have reported similar effects. For example, intracerebroventricular administration of CCK-antisense resulted in a decrease of anxiety in rats [34]. Interestingly, in healthy volunteers, CCK4, a selective CCK2 receptor agonist, is reported to produce panic attacks [12]. On the other hand, according to the reports of other investigators, CCK failed to produce anxiogenic effects [13,14]. van Megen et al. [2] have documented an anxiolytic rather than an anxiogenic effect for CCK8. These authors have shown a decrease in avoidance response, using the free operant avoidance paradigm in rats as well as a decrease in anxiety-like behavior. Comparable results were reported by Hsiao et al. [35] as well. The above controversial results could be due to individual and species differences, different methodological factors, specific receptor ligands, and different experimental conditions [36] or inability of CCK to cross blood brain barrier [37]. Moreover, the sites of injections also should be considered.

In the present experiment, bilateral intra-CA1 injection of LY225910, a selective CCK2 receptor antagonist [15] increased both %OAT and %OAE in EPM indicating that the drug produced significant anxiolytic behavior without significant changes in the locomotor activity. In support of our results it has been shown that CCK2 receptor antagonists can produce anxiolytic effects [14,47]. Moreover, in a previous study the PVG hooded rats treated with intraperitoneal administration of LY225910 showed an antianxiety response in the elevated plus-maze [15]. Furthermore, anxiogenic effect of CCK8s following intracerebroventricular administration, was prevented by blocking CCK2 receptors using selective CCK2 receptor antagonist but not selective CCK1 receptor antagonist [38]. Therefore, the data obtained in the present work, may show that the anxiogenic response induced by CCK8s is mediated through activation of CCK2 receptor mechanism. In support of our suggestion, intracerebroventricular administration of CCK8s, a selective CCK1 receptor agonist, did not affect the anxiety-related behaviors [38]. From the above results one may suggest that CCK2 receptor plays a physiological role in the modulation of anxiety in the dorsal hippocampus. The present results are in contrast to other studies that have shown CCK receptor antagonists, on their own, do not affect baseline anxiety behavior but they may instead “modulate heightened states of anxiety” [39,40]. Since it has been reported that CCK receptor antagonists do not have sedative, ataxic or anticonvulsant effects and do not produce dependence syndrome following withdrawal from chronic treatment [6], selective CCK2 receptor antagonists may be considered as potential candidates for antianxiety management.

In the present experiments, bilateral intra-CA1 injection of muscimol, selective GABA_A receptor agonist, produced significant dose dependent increase in %OAT and a slight increase in %OAE consistent with an antianxiety profile. This is in agreement with the results of Dalvi and Rodgers [24] that demonstrated antianxiety effects in mice following the intraperitoneal administration of muscimol and proposed that GABA_A receptor mechanisms can influence anxiety behavior in rodents. Such effects have been reported following the intracerebroventricular [25] and intra-amyg- data [23] injections of muscimol in rats as well.

Bicuculline, a selective GABA_A receptor antagonist, has generally been found not to have specific effects in animal models of anxiety [24]. In the present study, bilateral intra-CA1 injection of bicuculline produced no significant change in animal behavior in the elevated plus-maze. In another study from our laboratory, the intracerebroventricular administration of bicuculline in rats showed no effect on
animal behavior in the elevated plus-maze as well [25]. However, in contrast to the above reports, the injection of bicuculline in the basolateral amygdala has been shown to produce anxiogenic-like effects in social interaction paradigm and conflict paradigm [23]. In the same study, the injection of bicuculline into the central nucleus of the amygdala did not elicit any response, which is suggestive that bicuculline effects might depend on the site of the drug administration.

It has been proposed that interaction between CCK and GABA might also contribute to the etiology of anxiety disorders [41]. These two neurotransmitters are co-localized in several structures of the brain that control emotion and cognitive processing [2,41], see also Introduction]. GABA release in the brain has been shown to be influenced by CCK and vice versa [42,43]. Bourin and Vásar [41] have suggested that brain site directed injection of selective CCK and GABA drugs could give new insights into the role of interaction between two neurotransmitters in the regulation of fear and anxiety.

To investigate CCK and GABA interaction, we have injected (intra-CA1) muscimol 3 min after CCK_{8s}. When these animals were compared with the rats that received muscimol alone, no interaction was found. In agreement with these results, Fox et al. [44] have reported that CCK_{8s} could not block the discriminative properties of cholodiazoxide. In another study caerulein, a non-selective CCK1 and CCK2 receptor agonist, that on its own had anticonvulsant effect also did not change diazepam anticonvulsant effect [20].

The present data showed that bicuculline and CCK_{8s} with 3 min interval administration, failed to show interaction on %OAT, %OAE and locomotor activity. In agreement with these results, Biro et al. [45] demonstrated that bicuculline failed to affect CCK_{8s}-induced anxiogenesis following the intracerebroventricular administration. Finally, from the above results one may conclude that CCK may not have role in the anxiolytic effect of the GABAergic system nor does it affect on the anxiety baseline of the CA1 region of the hippocampus.

To study the interaction between CCK receptor antagonist and GABA_A receptor antagonist, we have injected intra-CA1, LY225910 and bicuculline with 3 min interval. When these groups were compared with the animals that received LY225910 alone, a significant interaction was found between the two drugs indicating a decrease in the anxiolytic action of LY225910. In another series of experiments, muscimol was replaced bicuculline. Animals in this experiment also received LY225910 after 3 min. Similar to the previous experiment, the results showed a significant interaction between muscimol and LY225910 that was manifested again as a reduction in the %OAT, indicating a decrease in the anxiolytic effect of the antagonist. However, %OAE was unchanged. In a similar pattern, it has been shown that LY225910 increased only %OAT but not %OAE [15]. It has also been reported that the drug induced an anxiolytic response. On the other hand, we have proposed previously that pre-synaptic blockade of either GABA_A or GABA_B may cause release of GABA [46]. Therefore, it can be suggested that low dose of the GABA receptor agonist may act on pre-synaptic GABA receptor sites and decrease the release of GABA. This in turn, may behave similar to bicuculline which reduces LY225910-induced antianxiety response. This may account for the response of muscimol in the present study as well. Further studies are needed to explain why both GABA_A agonist and antagonist have significantly reduced the anxiolytic action of LY225910. The similar confusing results have been reported by Chopin and Briley [9] who demonstrated that flumazenil, the benzodiazepine antagonist, antagonized both anxiogenic and anxiolytic effects induced by CCK_{8s} and L-365260 (selective CCK_{2} receptor antagonist) respectively. The results of the present study suggest that a GABA mechanism may be involved in the CCK_{2}-induced anxiolysis that is blocked by both bicuculline and muscimol. In agreement with this result, GV150023, a selective CCK_{2} receptor antagonist, which has antianxiety properties [47] not only prevented CCK facilitatory effects in the cerebral cortex but also primarily reduced GABA release in this region [48].

In conclusion, the intra-CA1 administration of CCK_{8s} resulted to an anxiogenic-like behavior contrary to the administration of LY225910 that produced anxiolytic effects. Moreover, we demonstrated the presence of an interaction between GABA and CCK systems in the modulation of anxiety in the CA1 region of the hippocampus. To clarify the exact mechanisms underlying the above complex interactions, more studies are required.

References


