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Differential contribution of cholecystokinin receptors to stress-induced modulation of seizure and nociception thresholds in mice

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Abstract

Recent evidence suggest that endogenous cholecystokinin (CCK) has important roles in central responses to stress. CCK receptors are known as functional modulators of opioidergic system with a tonic antiopioid effect in nociceptive pathways. In contrast, CCK receptor ligands are known to induce anticonvulsant effects similar to endogenous opioids. It is not clear whether endogenous CCK may play a role in the anticonvulsant effects of stress, especially in those stressful paradigms that are associated with strong activation of opioid pathways. The present study examined the role of endogenous CCK receptors in acute stress-induced modulation of seizure (clonic seizures induced by pentylenetetrazole) and nociception (tail-flick) thresholds. Acute restraint stress (for 2 h) and prolonged intermittent footshock stress (30 min) both induced opioid-dependent anticonvulsant and antinociceptive effects. While CCK receptor antagonist proglumide (10, 20, or 40 mg/kg) had no effect on seizure or nociception threshold by itself, it inhibited the anticonvulsant effects of both these types of stress while potentiating their antinociceptive effects. Moreover, proglumide exerted a similar inhibition of the anticonvulsant effect and potentiation of the antinociceptive effect of acute morphine at 1 mg/kg. In contrast, brief and continuos footshock stress (3 min) that induced a nonopioid type of antinociception did not increase the seizure threshold. Proglumide pretreatment did not alter any of these effects of brief footshock stress paradigm. The present data suggest that CCK receptors specifically and differentially modulate the opioid-mediated anticonvulsant and antinociceptive effects of acute stress.

Keywords: Opioid; Cholecystokinin; Restraint stress; Footshock stress; Seizure; Antinociception

1. Introduction

Stressful paradigms induce inhibitory effects on the susceptibility of experimental animals to seizure. In this regard, it has been reported that footshock (Soubrie et al., 1980; Drugan et al., 1985), restraint (De-Lima and Rae, 1991; Hashimoto et al., 2001), and swim stress (De-Lima and Rae, 1991; Peričić and Bujas, 1997; Peričić et al., 1999, 2000a, 2000b, 2001) can induce anticonvulsant effects against different kinds of seizures. Although stress affects many different systems in the brain, it is believed that endogenous protective mechanisms are involved in the inhibitory effects of stress against seizure (Shavit et al., 1984). Accordingly, acute stress augments the activity of brain γ-aminobutyric acid system (Schwartz et al., 1987; Akinci and Johnston, 1997) and endogenous opioid pathways have been implicated in the anticonvulsant effects induced by some types of stress (Oliverio et al., 1983; Shavit et al., 1984; Pavone et al., 1986). We have recently reported the opioid-mediated anticonvulsant effects of acute restraint and acute prolonged and intermittent footshock-stress paradigms in mice against pentylenetetrazole (PTZ)-induced clonic seizures (Homayoun et al., 2002a,b). However, the brief and continued footshock stress in the same environment that resulted in an opioid-independent type of antinociception (Lewis et al., 1980) did not alter the seizure susceptibility (Homayoun et al., 2002a).

In recent years, it has become evident that the antinociceptive effects of opioidergic pathways are functionally counterbalanced by endogenous cholecystokinin (CCK) receptors (Zelter, 1979; Faris et al., 1983; Watkins et al., 1985a,b; Suh et al., 1992; Rastegar et al., 2002). CCK receptors in the brain have striking distribution overlap with opioidergic pathways (Stengaard-Pedersen and Larsson, 1981; Gall et al., 1987) and have been implicated as

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an endogenous functional modulator of opioid effects (Zelter, 1980a; Faris et al., 1983; Zarrindast and Rezayat, 1994). Notably, CCK receptors seem to antagonize the antinociceptive effects of opioids provided opioid pathway has become active, while these receptors do not seem to play a tonic role in control of nociception (Friedrich and Gebhart, 2000). Interestingly, it seems that stressful situations facilitate the activation of antianalgesic CCK mechanisms, which in turn modulate opioid-mediated antinociception (Lavigne et al., 1992; Idanpaan-Heikkila et al., 1997; Hawranko and Smith, 1999; Hawranko et al., 1999). In contrary to their effects on antinociception, CCK receptor agonists have well-known anticonvulsant effects (Zetler, 1980b; Kadar et al., 1985, 1987) and have been reported to potentiate the anticonvulsant effects of morphine against maximal electroshock in rats (Legido et al., 1995). Moreover, CCK mRNA expression in hippocampus increases following stress (Giardino et al., 1999) and endogenous CCK pathway has been implied in stress-induced amnesia (Dauge et al., 2003). However, the role of endogenous CCK pathway in tonic regulation of seizure susceptibility by stress and its interaction with opioids in this regard has not been elucidated. To address this question, the present study compared the effects of CCK receptor blocker proglumide on the anticonvulsant and antinociceptive effects of acute restraint or footshock stress and exogenous administration of morphine. The results are suggestive of an opioid-dependent and differential modulation of seizure susceptibility by endogenous CCK receptors in stressful conditions.

2. Methods

2.1. Subjects

Male NMRI mice (Pasteur Institute of Iran) weighing 22–30 g were used. The animals were housed in temperature-controlled room ($24 \pm 2^{\circ}$) on a 12-h light/dark cycle with free access to food and water. All procedures were carried out in accordance with institutional guidelines for animal care and use. Each mouse was used only once and each treatment group consisted of seven animals.

2.2. Drugs

Drugs used were morphine sulfate and proglumide (Sigma, Poole, UK) and naloxone hydrochloride (Tolid-daru, Iran). Morphine and naloxone were dissolved in physiological saline solution to such concentrations that requisite doses were administered in a maximum volume of 10 ml/kg. Proglumide was dissolved in 10% dimethylsulfoxide/saline and its solvent was used as vehicle. All agents were administered intraperitoneally, except morphine, which was administered subcutaneously.

2.3. Stress

Restraint stress was induced by placing the mice in 25-mm inner diameter plastic tubes with suitable ventilation at one end, with the other side closed off. Animals were kept in restraint conditions for 30 min, 1 h, or 2 h between 10:00 a.m. and 15:00 p.m. and then were used for assessment of nociception and seizure threshold (Homayoun et al., 2002b). Footshock stress was induced using a wooden box ($30 \times 30 \times 40$ cm high) with a steel-rod floor (29 parallel rods, 0.3 cm in diameter set 1 cm apart). Inescapable footshock (3 mA scrambled shock stimulus, 50 Hz) was delivered through a scrambler to the grid floor (Madden et al., 1977; Lewis et al., 1980). Animals were exposed to one of the two procedures: (a) brief, continuos footshock for 3 min or (b) prolonged, intermittent footshock for 30 min (1-s pulses delivered every 5 s). Animals were allowed to acclimatize with the apparatus for 20 min on the day before stress induction (Homayoun et al., 2002a).

2.4. Assessment of antinociception

Stress-induced analgesia was assessed by tail-flick test (D'Amour and Smith, 1941). The animals were briefly restricted by a restrainer with their tail positioned in an apparatus (type 812, Hugo Sachs Electronics, Germany) for radiant heat stimulation on the dorsal surface of the tail. Tail-flick latency was defined as the time interval between the application of a standardized beam focused on to the tail and the abrupt removal of the tail from the nociceptive stimulus. The cut-off time was 6 s. The results were expressed as "percent maximum possible effect" (%MPE), which was calculated as follows: %MPE=(poststress latency − baseline latency) × 100/(cut-off latency − baseline latency). Baseline latency was the mean of the two measurements carried out between 60 and 30 min before the start of the stress session and poststress measurements were carried out 5 min after stress session in restraint stress and 2–5 min after removal from shock environment in footshock stress experiments.

2.5. Assessment of seizure threshold

PTZ-induced clonic seizure threshold was assessed by inserting a 30-gauge stainless steel needle in mice lateral tail vein, which was secured to the tail by a narrow piece of adhesive tape. The PTZ solution (1.0%) was infused into the tail vein of the freely moving mouse at constant rate of 0.5 ml/min. Infusion was halted when forelimb clonus followed by full clonus of the body was observed. The minimal dose of PTZ (mg/kg of mice weight) needed to induce clonic seizure was measured as an index of seizure threshold. The seizure threshold was assessed 5 min after the termination of footshock stress and 15 min after the termination of restraint stress.

2.6. Treatment

The first part of the experiment assessed the effects of acute restraint stress on nociception and seizure threshold. Three different durations of restraint (30 min, 1 h, or 2 h) were used, and based on the results, a 2-h duration was used for drug experiments. Naloxone (0.3 or 1 mg/kg) was administered 1 min before testing either to mice subjected to a 2-h restraint or to control nonstressed mice. The second experiment examined the effect of proglumide on restraint-stress-induced changes in seizure and nociception threshold. Proglumide (10, 20, or 40 mg/kg) or its vehicle were administered 15 min before a 2-h restraint session or a similar duration of nonstress presence in the home cage. Experiment 3 examined the effect of proglumide on foot-shock stress of morphine (1 mg/kg) modulation of seizure and nociception thresholds. Controls in this experiment received vehicle or proglumide (40 mg/kg) 60 min before tail-flick test. Two groups received the same pretreatment

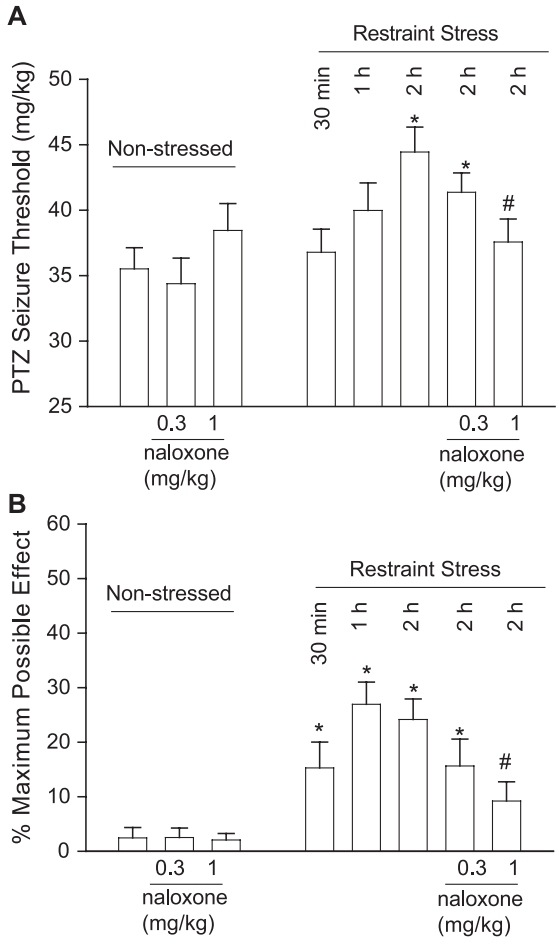

Fig. 1. The effect of acute restraint stress on modulation of seizure and nociception threshold in mice. Different durations of restraint stress (30 min to 2 h) induced time-dependent anticonvulsant (A) and antinociceptive (B) effects that were reversible by opioid receptor antagonist naloxone (0.3 or 1 mg/kg). * $P<.05$ compared with nonstressed control group. # $P<.05$ compared with 2-h restraint-stressed group.

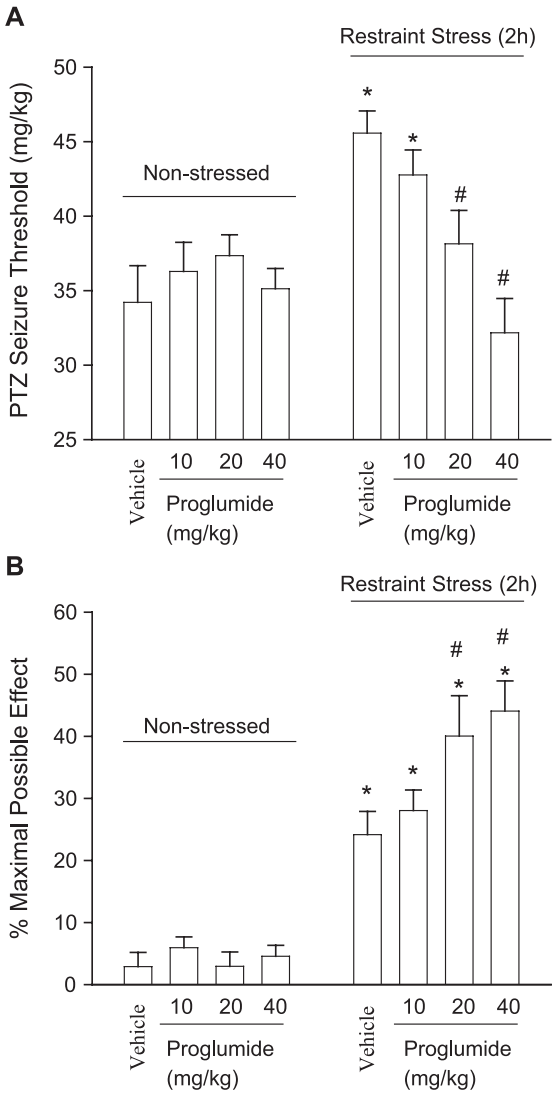

Fig. 2. The differential effects of proglumide on restraint stress-induced anticonvulsant and antinociceptive effects. Proglumide (10, 20, or 40 mg/kg) or its vehicle did not affect either seizure threshold or tail-flick latency in nonstressed conditions. However, proglumide induced significant inhibition of restraint stress-induced anticonvulsant effect (A) while potentiating the antinociceptive effect of acute restraint stress (B). * $P<.05$ compared with vehicle-treated nonstressed control group. # $P<.05$ compared with vehicle-treated stressed group.

followed by morphine (1 mg/kg) administration 40 min before tail-flick test. Two other groups received similar vehicle or proglumide pretreatment, and then 30 min later, were placed in the footshock environment for 30 min prolonged footshock. Two other groups received the same pretreatment but only received a 3-min brief and continuous footshock immediately before tail-flick test.

2.7. Statistical analysis

Data are expressed as mean ± S.E.M of either PTZ seizure threshold or percent maximum possible antinociceptive effect. Statistical comparison between more than two

groups was done by one-way analysis of variance followed by post hoc Student–Newman–Keuls test. A P value $<.05$ was considered significant.

3. Results

3.1. The effect of restraint stress on seizure and nociception thresholds

As shown in Fig. 1, acute restraint stress induced significant time-dependent anticonvulsant and antinociceptive effects. Restraint stress for 2 h (but not for shorter durations of 30 min or 1 h) induced a significant anticonvulsant effect that was reversible by naloxone pretreatment (0.3 and 1 mg/kg) (Fig. 1A) [$F(7,48)=4.41$, $P<.001$]. However, even a 30-min restraint stress could significantly increase the antinociception threshold compared to non-stressed condition (Fig. 1B) [$F(7,48)=7.99$, $P<.001$]. The maximum stress-induced antinociception was observed with 1-h stress duration, although 2-h stress duration still induced a high level of antinociception. Again, naloxone reversed the stress-induced antinociception completely. It should be noted that throughout this study, %MPE was used as an index for antinociception. Analysis of baseline tail-flick latency values did not show any significant difference between groups (data not shown, mean ± S.E.M. = 2.79 ± 0.09 for control nonstress group).

3.2. The effect of proglumide on restraint stress-induced anticonvulsant and antinociceptive effects

As shown in Fig. 2, proglumide (10, 20, or 40 mg/kg) or its vehicle did not affect the seizure (Fig. 2A) or nociception (Fig. 2B) thresholds. However, proglumide decreased the anticonvulsant effect of acute 2 h restraint stress compared to vehicle-treated group [$F(7,48)=4.63$, $P<.001$]. The reversal was complete with higher doses of the CCK receptor antagonist (20 or 40 mg/kg). In contrast, proglumide dose-dependently potentiated the antinociceptive effect of restraint stress [$F(7,48)=22.44$, $P<.001$].

3.3. The effect of proglumide on footshock stress and morphine-induced modulation of seizure and nociception threshold

As shown in Fig. 3, the effect of pretreatment by an effective dose of proglumide (40 mg/kg) on opioid-related modulation of pain and seizure was assessed. Morphine at 1 mg/kg induced a strong anticonvulsant and mild antinociceptive effect. Pretreatment with proglumide significantly inhibited the anticonvulsant effect of morphine (Fig. 3A) [$F(3,24)=11.33$, $P<.001$] but potentiated its antinociceptive effect (Fig. 3B) [$F(3,24)=34.81$, $P<.001$]. We further examined the effect of proglumide

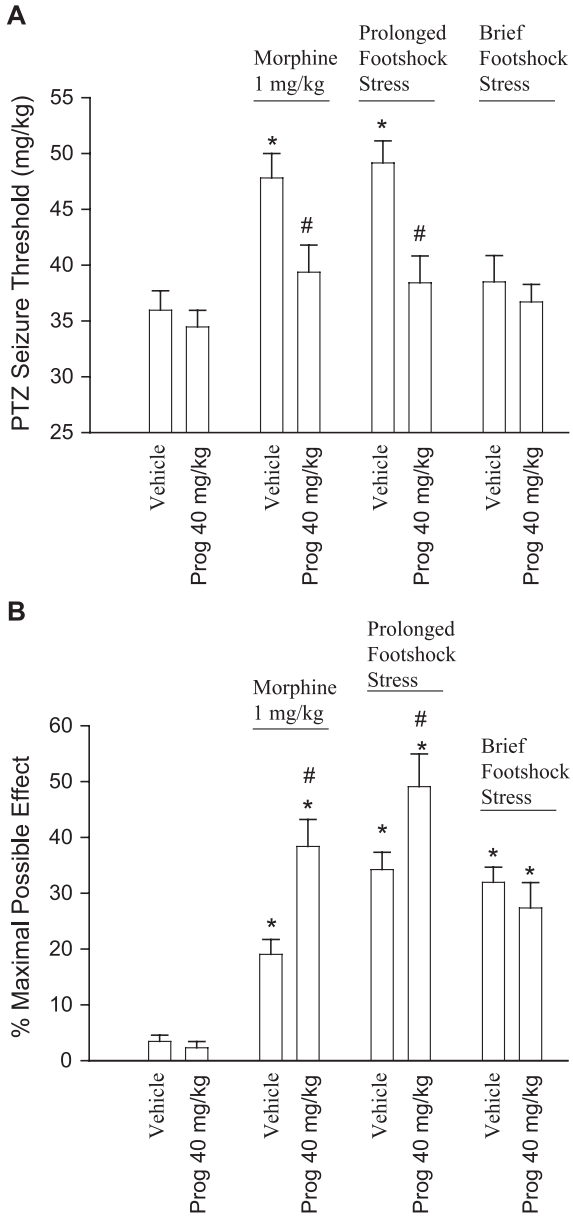

Fig. 3. The effect of endogenous CCK receptor antagonism on morphine- and footshock stress-induced modulation of seizure and nociception threshold. Proglumide (40 mg/kg) did not affect seizure or nociception threshold by itself but reversed the anticonvulsant effects of morphine (1 mg/kg) or opioid-dependent prolonged intermittent footshock stress without affecting the seizure threshold in mice subjected to brief and continuous footshock stress (A). In contrast, proglumide significantly potentiated the antinociceptive effects of morphine and prolonged footshock stress, again without affecting the non-opioid-mediated antinociceptive effect of brief footshock stress (B). $^{*}P<.05$ compared with vehicle-treated nonstressed control group. $^{\#}P<.05$ compared with corresponding vehicle-treated group.

on two distinct paradigms of footshock stress. As we have recently reported, prolonged and intermittent footshock induces opioid-mediated anticonvulsant and antinociceptive effects, while brief and continuos footshock induced a non-opioid-mediated type of antinociception without any anticonvulsant effect (Homayoun et al.,

2002a, data not shown). Pretreatment with proglumide in mice subjected to prolonged footshock stress, significantly inhibited the anticonvulsant (Fig. 3A) [$F(3,24)=18.62$, $P<.001$] effect of stress, while in the same animals potentiated the antinociceptive effect of stress (Fig. 3B) [$F(3,24)=46.88$, $P<.001$]. In contrast, proglumide failed to affect the seizure threshold in mice subjected to brief footshock stress (Fig. 3A) [$F(3,24)=1.7$, $P>.05$] and did not alter the antinociceptive effect of this type of stress (Fig. 3B) [$F(3,24)=32.05$, $P<.001$, post hoc comparison $P>.05$].

4. Discussion

The present study reports the differential interaction of endogenous CCK receptors with the anticonvulsant and antinociceptive effects of acute stress in mice. The present results suggest that CCK pathway becomes activated in the presence of either exogenous opioid or in opioid-mediated types of stress, and as a result, exerts an antiopioid effect in the control of nociceptive threshold but an agonistic effect with endogenous opioid system in control of seizure threshold. The tonic role of CCK receptors in the anticonvulsant effects of those stressful paradigms that activate opioidergic system may be part of an endogenous protective mechanism.

The anticonvulsant effect of acute stress in the current study is in agreement with previous reports (Soubrie et al., 1980; Drugan et al., 1985; De-Lima and Rae, 1991; Peričić et al., 1999). In the restraint model, the anticonvulsant effect, in parallel to previously reports on stress-induced analgesia, was dependent on the duration of restraint and was blocked by opioid receptor antagonist (Bhattacharya et al., 1978; Pilcher and Browne, 1983; Kelly and Franklin, 1987). Meanwhile, it is known that opioid-mediated regulation of stress antinociception can be affected by alterations in CCK-related mechanisms (Lavigne et al., 1992; Idanpaan-Heikkila et al., 1997; Hawranko et al., 1999). CCK receptors exert the role of an endogenous antiopioid system in the regulation of nociception while opioid system has become activated by exogenous or endogenous mechanisms (Lavigne et al., 1992; Idanpaan-Heikkila et al., 1997; Friedrich and Gebhart, 2000; Rastegar et al., 2002). In the current study, proglumide significantly potentiated the stress-induced antinociception, in accordance with a tonic pronociceptive role for endogenous CCK receptors. Interestingly, in modulation of seizure susceptibility, CCK receptor agonists show anticonvulsant effects against different kinds of seizures (Zetler, 1980b; Kadar et al., 1985, 1987). In the present study, proglumide did not alter the seizure threshold by itself suggesting that endogenous CCK pathways are not involved in the tonic regulation of seizure susceptibility. However, proglumide significantly decreased the restraint stress-induced anticonvulsant effect, pointing to the protective role of the endogenous CCK mechanisms activated during stress. The role of CCK mechanisms in the modulation of seizure susceptibility by stress has not been previously examined, but the present data and the fact that CCK and opioid pathways are strongly colocalized and functionally related (Stengaard-Pedersen and Larsson, 1981; Gall, 1988; Gall et al., 1987) is suggestive of a possible agonistic opioid–CCK interaction activated by acute stress. In fact, Legido et al. (1995) have shown that CCK may act as an endogenous agonist with opioids in regulation of predominantly brainstem controlled generalized tonic–clonic seizures (Gale, 1992; Eells et al., 2004). The present data on dominantly forebrain-regulated PTZ-induced clonic seizures extends the potential foci for such agonistic interactions to the epileptogenic centers of forebrain areas, such as piriform cortex, a center with the highest labeling for CCK mRNA in brain (Ingram et al., 1989). Moreover, recent reports of a direct CCK-mediated pathway to thalamus controlling hypothalamic stress axis are of special interest in this regard (Bhatnagar et al., 2000; Abelson and Young, 2003).

We further observed that proglumide pretreatment could substantially attenuate the effect of a strong anticonvulsant dose of morphine (1 mg/kg). However, the same dose of CCK receptor antagonist induced a reverse potentiating effect on the mild antinociceptive effect of the same dose of morphine, further demonstrating that two systems have distinct interactions in separate brain regions responsible for regulation of pain and seizure threshold (Legido et al., 1995; Friedrich and Gebhart, 2000). However, the appearance of a protective anticonvulsant effect for endogenous CCK pathways in the presence of morphine suggests that opioids may control CCK release in seizure-regulating areas in a similar fashion as they control CCK release in nociceptive pathways, although with opposite functional significance. To further examine the hypothesis that a tonic anticonvulsant CCK-mediated pathway may be specifically activated in parallel to opioid system in certain stressful conditions, we used two types of footshock stress known to induce opioid and nonopioid types of antinociceptive response (Lewis et al., 1980; Homayoun et al., 2002a). Proglumide selectively potentiated the opioid-mediated prolonged footshock stress analgesia without affecting the non-opioid-mediated analgesic effect of brief footshock stress. At the same time, proglumide also decreased the anticonvulsant effect of prolonged footshock stress without altering the seizure-threshold in mice subjected to brief stress. Together with restrains stress experiments, these data support a differential interaction between CCK and opioid pathways in regulation of seizure and nociception thresholds in stressful conditions. This includes an agonistic interaction in regulation of clonic seizure susceptibility, at least during stressful conditions that are associated with increased opioidergic tone.

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