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CGRP Prevents Electroconvulsive Shock-Induced Amnesia in Rats

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KOVÁCS, A. AND G. TELEGDY. *CGRP prevents electroconvulsive shock-induced amnesia in rats.* PHARMACOL BIOCHEM BEHAV **47**(1) 121–125, 1994.—The effects of calcitonin gene-related peptide (CGRP) on electroconvulsive shock (ECS)-induced amnesia and the possible involvement of neurotransmitters in this action were studied in rats. ECS-induced amnesia was elicited in a passive avoidance paradigm. The possible roles of different transmitters involved in mediating CGRP action were followed by pretreating the animals with different receptor blockers in doses which themselves could not influence the paradigm. CGRP facilitated learning in the passive avoidance paradigm and prevented ECS-induced amnesia in a dose-dependent manner. Pretreatment with atropine, naloxone, phenoxybenzamine, or propranolol blocked the antiamnesic action of CGRP. Other receptor blockers, such as bicuculline, methysergide, and haloperidol, were ineffective. The results support our previous finding that CGRP facilitates passive avoidance learning and prevents ECS-induced amnesia. In the antiamnesic action of CGRP, cholinergic, opiate, and α- and β-adrenergic mediators are involved.

CGRP ICV administration ECS-induced amnesia Passive avoidance behaviour Transmitter mediation

CALCITONIN gene-related peptide (CGRP) was discovered by molecular geneticists (3,4,35). This neuropeptide is widely distributed in the peripheral (13,34,36,39,46,50) and central nervous system of rats (21,38,40,52) and man (15). It is present in the cerebrospinal fluid (53) and plasma (17,51,54). Specific binding sites have been described in the rat brain (37,52). The immunocytochemical data were confirmed by in situ hybridization (25). Intracerebroventricular (ICV) administration of CGRP was found to inhibit food intake (24,42), gastric acid secretion, and gastric emptying (28,29,33,41). It has also been reported that CGRP reduces locomotion, has dose-related effects on rectal temperature, and causes cataleptogenic effects (10,20) and nociception (20). The present article is a continuation of work in which we have found that CGRP introduced into the lateral brain ventricle increased the latency of passive avoidance response (23) when it was given immediately after the learning trial; thus, CGRP facilitated the consolidation of passive avoidance learning. In this action, β-adrenergic, serotonergic, and opiate receptors were involved (22). In the present experiments, the action of CGRP on shock (ECS)-induced amnesia and the possible involvement of neurotransmitters were studied in rats.

METHODS

Animals and Surgery

CFY male rats weighing 150–200 g were housed six per cage in a light- and temperature-controlled room (lights on 0600–1800; 23°C) and had free access to food and water. A stainless steel cannula was implanted into the lateral brain ventricle under pentobarbital-Na anaesthesia (Nembutal 35 mg/kg IP). The cannula was fixed with dental cement and acrylate resin. The animals were used in experiments after a recovery period of five days. The correct positioning of cannula was checked by dissection of the brain. The experiments were performed in the morning.

Experimental Apparatus and ECS

The rats were trained in a one-trial learning passive avoidance apparatus (1). An illuminated runway was (7 × 30 cm) was attached to a dark box (37 × 30 × 25 cm). After a 3-min dark adaptation, the animals were placed on the illuminated runway three times (first day). Since the animals prefer dark to light, they usually entered the dark box within 15 min. Two other sessions were given on the next day. After the second entry of the animals, unavoidable foot shock (0.5 mA, 2 s) was delivered through the grid floor of the dark compartment. Immediately after this learning trial, the animals were removed from the dark box, and retrograde amnesia was induced by ECS via ear clip electrodes using a MINICOMA (AC 190 V, 50 Hz, 0.5 s duration, position 2) apparatus. The control animals received no ECS.

Pretreatment by Receptor Blockers

The following receptor blockers were given 30 min before the learning trial: atropine (EGYT, Budapest) (2 mg/kg IP), bicuculline (Serva, Heidelberg, Germany) (1 mg/kg IP), ha-

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loperidol (G. Richter, Budapest) (5 μg/kg IP), methysergide (Sandoz, Basel, Switzerland) (5 mg/kg IP), naloxone (Endo Lab Inc, Garden City, NY) 0.3 mg/kg IP), phenoxybezamine (Smith, Kline and French, Philadelphia) (2 mg/kg, IP), and propranolol (ICI Ltd, Macclesfield, Cheshire, England) (10 mg/kg IP).

Peptide Administration

CGRP (Bachem, Torrance, CA) was dissolved in 0.9 percent NaCl and injected in a dose of 300 ng, 500 ng, or 1 μg in a volume of 4 μl into the lateral brain ventricle, immediately after the ECS-induced amnesia. The control animals received physiological saline. The animals were tested 24 and 48 h after the treatment.

Statistical Analysis

The data were analysed by analysis of variance (ANOVA), followed by Tukey's test. A p value of 0.05 or less was considered statistically significant.

RESULTS

The avoidance latency of animals treated with foot shock and saline was approximately 130 s (mean). If the animals received ECS, the avoidance latency decreased significantly ($p < 0.05$ vs. foot shock). CGRP in a dose of 300 ng (ICV) had no significant action. Five hundred nanograms and 1 μg CGRP antagonized ECS-induced amnesia ($p < 0.05$ vs. amnesia) at 24 and 48 h (Fig. 1). For further experiments, the dose of 1 μg/rat was selected and the animals were tested only 24 h after treatment.

Pretreatment With Receptor Blockers

The doses of receptor blockers were chosen in accordance with previous experience that the receptor blocker itself did not influence the passive avoidance paradigm, but blocked the action induced by a number of neuropeptides (43). Atropine, naloxone, phenoxybenzamine, and propranolol inhibited CGRP-induced amnesia, $F(4, 45) = 18.20, 8.84, 28.61, 17.08$, respectively, $p = 0.0001$ in all cases (Table 1). Bicuculline, haloperidol, and methysergide, $F(4, 45) = 14.14$, $F(4, 45) = 17.03$, $F(4, 84) = 16.71$, respectively, $p = 0.0001$ in all cases, did not change the antiamnestic effect of the peptide.

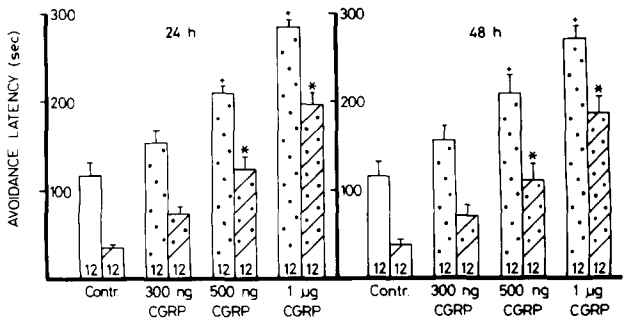

FIG. 1. The effects of CGRP in different doses on ECS-induced amnesia. □ control, ▨ amnesia, ▣ control + CGRP, ▩ amnesia + CGRP. Number of animals in bars. The values are mean ± SE. The F value of the 24-h test is in ANOVA, $F(7, 88) = 37.99$, $p = 0.0001$. The F value of the 48-h test is in ANOVA, $F(7, 88) = 23.44$, $p = 0.0001$. $^*p < 0.05$ vs. amnesia, $^+p < 0.05$ vs. control.

DISCUSSION

This study confirmed previously reported data that CGRP can improve the consolidation of a passive avoidance response (23). It seems (from our earlier experiments) that the action of CGRP can be modified by β-adrenergic, serotonergic, and opiate receptor blockers (22). Other receptor blockers, such as cholinergic, dopaminergic, α-adrenergic, and GABAergic blockers, were ineffective in the doses used. The doses of receptor blockers were in all cases selected in accordance with previous findings that these doses were effective in blocking the similar action of other peptides (8,43,47), but did not modify the task itself. Following this experience, in the present study we demonstrated that CGRP blocked the amnesia caused by ECS in a passive avoidance paradigm. This finding provides further evidence on the enhancing effects of CGRP in learning and memory formation. It is interesting that the antiamnesic action of CGRP is mediated not only by β-adrenergic and opiate receptors, but also by cholinergic and α-adrenergic receptors. Serotonergic mediation is not involved in this action. The difference in transmitter systems in mediating the simple passive response and the antiamnesic action of CGRP in the same paradigm suggests that the mechanisms of the simple learning procedure and antiamnesia are different.

As concerns the involvement of different transmitters in CGRP action, very little is known. The coexistence of CGRP with neurotransmitters and/or neuropeptides is evidence of possible interactions. Motor neurons at the spinal and supraspinal levels contain acetylcholine (7,11,12,31) and CGRP. It has been shown in monkeys that CGRP-like immunoreactivity (CGRP-LI) is present in nerve endings in the ventral horn surrounding motor neurons containing serotonin (5,6).

Dopamine cells of the posterior thalamus contain CGRP-LI (32). CGRP coexists with encephalin in the lateral superior olivary nucleus (44). The presence of CGRP in a number of brain structures involved in learning phenomena (hippocampus, hypothalamus, thalamus, cerebellum, etc.) (2,9,18,26,45) is morphological evidence of the possibility that CGRP is involved in learning procedures. Besides CGRP-transmitter coexistence, a number of reports demonstrate that CGRP coexists with peptides too. In motor neurons, especially in development CGRP, somatostatin, vasoactive intestinal polypeptide, and galanin are present (16,30,48,49). Sensory neurons containing CGRP (19) also contain substance P (7,14,27, 30,39,50).

The learning of a passive avoidance response or the mechanism in which ECS-induced amnesia is blocked by CGRP is a rather complex behavioral reaction. It involves arousal, attention, motivation, motor coordination, and biochemical processes which lead to consolidation of the learned signal (i.e., memory formation). ECS blocks memory formation by a mechanism that is not fully understood. It is obvious that neurotransmitters are involved in both procedures, since the action of CGRP can be blocked by certain receptor blockers. As CGRP is associated with other neuromediators/neurotransmitters, it is possible that CGRP may act via transmitters which might mobilize some other peptidergic transmission as the last chain of the events. We have shown earlier that somatostatin improves passive avoidance learning and prevents ECS-induced amnesia (47).

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TABLE 1

THE EFFECTS OF DIFFERENT RECEPTOR BLOCKERS ON ANTIAMNESIC ACTION OF CGRP (1 μg ICV) IN RATS

Blockers	Avoidance Latency	Significance	
Atropine (2 mg/kg IP)			
Control (10)	131.9 ± 17.00		
Amnesia (10)	40.3 ± 7.05	vs. control	$p < 0.05$
Amn + Atropine (10)	56.9 ± 8.67		
Amn + CGRP (10)	202.1 ± 22.62	vs. amnesia	$p < 0.05$
Amn + Atropine + CGRP (10)	78.7 ± 16.24	vs. (amn + CGRP)	$p < 0.05$
Bicuculline (1 mg/kg IP)			
Control (10)	136.2 ± 24.9		
Amnesia (10)	47.3 ± 8.49	vs. control	$p < 0.05$
Amn + Bicuculline (10)	49.5 ± 7.52		
Amn + CGRP (10)	216.8 ± 27.60	vs. amnesia	$p < 0.05$
Amn + Bicuculline + CGRP (10)	204.2 ± 28.69		
Haloperiodol (5 μg/kg IP)			
Control (10)	128.7 ± 18.33		
Amnesia (10)	43.9 ± 7.83	vs. control	$p < 0.05$
Amn + Haloperidol (10)	58.3 ± 10.20		
Amn + CGRP (10	212.1 ± 24.64	vs. amnesia	$p < 0.05$
Amn + Haloperidol + CGRP (10)	225.6 ± 31.2		
Methysergide (5 mg/kg IP)			
Control (18)	127.0 ± 15.22		
Amnesia (18)	48.8 ± 7.75	vs. control	$p < 0.05$
Amn + Methysergide (17)	57.6 ± 6.69		
Amn + CGRP (18)	200.6 ± 21.23	vs.amnesia	$p < 0.05$
Amn + Methysergide + CGRP (18)	158.6 ± 21.39		
Naloxone (0.3 mg/kg IP)			
Control (10)	131.2 ± 26.66		
Amnesia (10)	42.6 ± 10.37	vs. control	$p < 0.05$
Amn + Naloxone (10)	60.2 ± 8.11		
Amn + CGRP (10)	174.9 ± 29.60	vs. amnesia	$p < 0.05$
Amn + Naloxone + CGRP (10)	55.3 ± 10.37	vs. (amn + CGRP)	$p < 0.05$
Phenoxybenzamine (2 mg/kg IP)			
Control (10)	126.7 ± 18.29		
Amnesia (10)	42.2 ± 7.76	vs. control	$p < 0.05$
Amn + Phenoxybenzamine (10)	54.6 ± 10.49		
Amn + CGRP (10)	208.2 ± 23.37	vs. amnesia	$p < 0.05$
Amn + Phenoxybenzamine + CGRP (10)	16.2 ± 5.03	vs. (amn + CGRP)	$p < 0.05$
Propranolol (10 mg/kg)			
Control (10)	126.3 ± 21.05		
Amnesia (10)	46.8 ± 8.38	vs. control	$p < 0.05$
Amn + Propranolol (10)	50.5 ± 10.44		
Amn + CGRP (10)	207.2 ± 26.01	vs. amnesia	$p < 0.05$
Amn + Propranolol + CGRP (10)	59.1 ± 9.99	vs. (amn + CGRP)	$p < 0.05$

Mean ± SE. Numbers in parentheses represent the number of animal used.

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