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Activation of Adenosine A_{2A} Receptor Impairs Memory Acquisition but not Consolidation or Retrieval Phases

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Abstract – Several lines of evidence indicate that adenosine A_{2A} agonist disrupts spatial working memory. However, it is unclear which stages of learning and memory are affected by the stimulation of adenosine A_{2A} receptor. To clarify these points, we employed CV-1808 as adenosine A_{2A} agonist and investigated its effects on acquisition, consolidation, and retrieval phases of learning and memory using passive avoidance and the Morris water maze tasks. During the acquisition phase, CV-1808 (2-phenylaminoadenosine, 1 and 2 mg/kg, i.p.) decreased the latency time in passive avoidance task and the mean savings in the Morris water maze task, respectively. During the consolidation and retrieval phase tests, CV-1808 did not exhibited any effects on latency time in passive avoidance task and the mean savings in the Morris water maze task. These results suggest that CV-1808 as an adenosine A_{2A} agonist impairs memory acquisition but not consolidation or retrieval.

Keywords: CV-1808, Adenosine A_{2A} receptor, Acquisition, Consolidation, Retrieval.

INTRODUCTION

Adenosine is a ubiquitous neuromodulator in the central nervous system (CNS). Its major roles in the CNS are to modulate neurotransmitter release, postsynaptic components, and nonsynaptic components, such as, glial cell signaling. Adenosine exerts its diverse physiological effects via the activations of specific G protein-coupled receptors, such as, the A_1, A_{2A}, A_{2B}, and A_3 receptors (Fredholm *et al*., 1994). Adenosine analogues exhibit various behavioral effects, which include, sedative effects (Barraco *et al*. 1983; Spealman and Coffin 1986), anticonvulsant activity (Dragunow, 1988), antinociceptive effects (Post 1984; Ahlijanian and Takemori 1985), conditioned avoidance response (Martin *et al*. 1993), and changes in cognitive functions (Winsky and Harvey 1986). Recently, xanthine, an adenosine A_{2A} antagonist, has received attention as a candidate treatment for Parkinson's disease (Kanda *et al*., 1998; Shiozaki *et al*., 1999; Koga *et al*., 2000), and xanthine derivatives have been reported to act as cognition enhancers (Von Lubitz *et al*., 1993). Although the memory related effects of adenosine analogues have been extensively studied (Wang *et al*., 2006; Mihara *et al*., 2007; Takahashi *et al*., 2008), relatively little attention has been paid to the possibility that adenosine A_{2A} receptor agonists or antagonists modulates memory processes. Therefore, the determination of the pharmacological effects of adenosine A_{2A} receptor on memory-related behaviors has become an important topic for those developing anti-amnesic agents.

There are three stages for learning and memory processing, namely, acquisition, consolidation, and retrieval (Abel and Lattal, 2001). Certain types of sensory system sourced information are rapidly encoded and may pass into labile memory, which may then be consolidated into long-term memory during the consolidation process. The final stage involves retrieval, which utilizes consolidated and fixed memory. Because compounds that improve cognitive processes, such as, acquisition, consolidation, and retrieval processes, are potentially useful for the treatment of memory deficits, it is important that the effects of such compounds on each phase of memory processing be determined (Prickaerts *et al*., 2005). Therefore, if the activation of adenosine A_{2A} receptor impairs these three learning and memory processes, it becomes a useful target for mnemonic agent develop-

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ment.

In the present study, we employed CV-1808 (2-phenylaminoadenosine) as an adenosine A_{2A} agonist and tested its effect on memory acquisition, consolidation, and retrieval using passive avoidance and the Morris water maze tasks.

MATERIALS AND METHODS

Animals

Male ICR mice weighing 25-30 g were obtained from the Orient Co., Ltd, a branch of Charles River Laboratories (Seoul). All animal procedures were conducted in accordance with the Principle of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) and were approved by the Institutional Animal Welfare Committee. Mice were housed 5 per cage in a housing room maintained at a constant temperature (23±1^{o}C) and humidity (60±10%), and under a 12-h light/ dark cycle (light on 07.30 - 19.30 h). Food and water were available ad libitum at all times except during testing. All behavioral tasks were conducted between 10:00 h and 16:00 h.

Passive avoidance task

Passive avoidance was carried out in identical illuminated and non-illuminated boxes (Gemini Avoidance System, San Diego, USA). The illuminated compartment (20 ×20×20 cm) contained a 50 W bulb. The non-illuminated compartment had a floor (20×20×20 cm) composed of 2 mm stainless steel rods spaced 1 cm apart. These two compartments were separated by a guillotine door (5×5 cm). For the acquisition trial, mice were initially placed in the illuminated compartment and the door between the two compartments was opened 10 s later. When mice entered the dark compartment, the door automatically closed and an electrical foot shock (0.5 mA) of 3 s duration was delivered through the stainless steel rods. Twenty-four hours after the acquisition trial, mice were again placed in the illuminated compartment to test retention. The time taken for a mouse to enter the dark compartment after the door opened was defined as latency. If a mouse did not enter the dark compartment within 300 s, it was assumed that the mouse had remembered the single 'acquisition' trial experience.

Mice received either vehicle (normal saline, i.p.) or CV-1808 (Tocris, UK) (0.25, 0.5, 1, or 2 mg/kg, i.p.) 30 min before the acquisition trial, immediately after acquisition trial, or 30 min before retention trial to examine its effects on acquisition, consolidation, and retrieval, respectively.

Morris water maze task

The Morris water maze task was carried out as described elsewhere (Collinson *et al*., 2006). Acquisition and retrieval sessions were conducted as described in Fig. 1. Before the first experimental day, mice were dedicated to swimming training for 60 s in the absence of the platform. On the following day, the mice were given four trials with the platform in place during the acquisition session. When a mouse located the platform, it was permitted to remain on it for 10 s and was then placed in a holding cage for 30 s (inter trial interval, ITI) until the start of the next trial. If the mouse did not locate the platform within 60 s, it was placed on the platform for 10 s. At the end of the ITI, the mouse was again placed into the pool but at a different location; and upon release, the next trial began. This procedure was repeated until four trials had been completed. Retrieval session was conducted 24 h after the fourth trial of acquisition session. During the

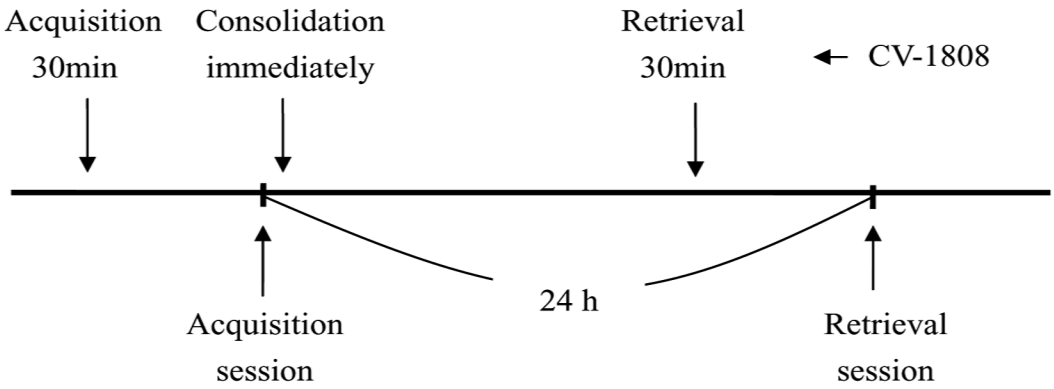

Fig. 1. Study design schematic. CV-1808 was administered 30 min before the acquisition session to determine its effects on acquisition memory, immediately after the acquisition session for consolidation memory, or 30 min before retrieval session for retrieval memory. A 24 h period was allowed between acquisition trials (acquisition session) and retention trials (retrieval session) for both the passive avoidance and Morris water maze tasks.

retrieval session, the mice were given one trial with the platform. The improvement in the animal's memory was calculated by subtracting the latency to find the platform during the retrieval session from the mean latency to find the platform for all 4 trials of acquisition session to give the savings score (Collinson *et al*., 2006). The following measurements were taken and analyzed using the video-based Ethovision System (Nodulus, Wageningen, The Netherlands): escape time of each session and swimming speed of retrieval session in the Morris water maze test. Mice received injections of either vehicle (normal saline, i.p.) or CV-1808 at various dosages (0.25, 05, 1, or 2 mg/kg, i.p.) 30 min before the first trial of acquisition session, immediately after acquisition session, or 30 min before retrieval session to examine its effects on acquisition, consolidation, and retrieval, respectively.

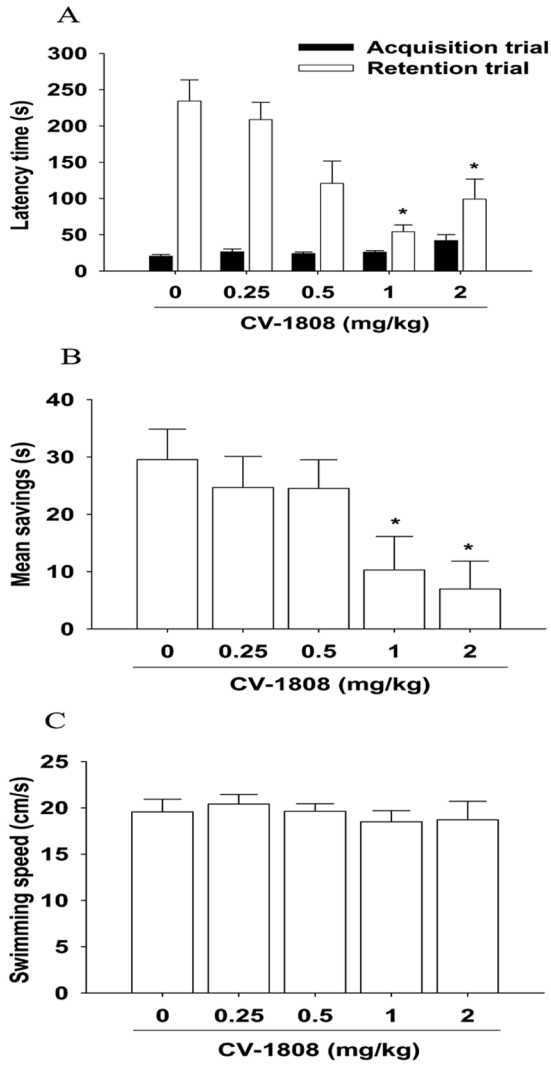

Fig. 2. Effect of CV-1808 (0.25, 0.5, 1, or 2 mg/kg, i.p.) on the acquisition phase of the passive avoidance task (A) and the Morris water maze task (B, mean savings; C, swimming speed). Task performances were evaluated as described in Materials and Methods. Data represent means ± SEM (n = 10/group) (*P < 0.05 versus vehicle control group).

Statistics

Values are expressed as means ± S.E.M. For the passive avoidance and the Morris water maze tests, data were analyzed by one-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls test for multiple comparisons. Statistical significance was set at $P < 0.05$.

RESULTS

Effect of CV-1808 on memory acquisition

To investigate the effect of CV-1808 on memory acquisition, we conducted passive avoidance and the Morris water maze tasks using pre-acquisition treatment study. CV-1808 (0.25, 0.5, 1, or 2 mg/kg, i.p.) was treated 30 min before the acquisition trial of passive avoidance task or the first training trial of acquisition session of Morris water maze task. In the passive avoidance task, CV-1808 (1 and 2 mg/kg, i.p.) significantly shortened latency time compared with control group ($P < 0.05$, Fig. 2A). Moreover, CV-1808 (1 and 2 mg/kg, i.p.) also significantly decreased the mean savings score in the Morris water maze task ($P < 0.05$, Fig. 2B). However, CV-1808 did not change the latency time in the acquisition trial in the passive avoidance task (Fig. 2A) and the swimming speed in the Morris water maze task (Fig. 2C), indicating that CV-1808 did not affect any behavioral changes.

Effect of CV-1808 on memory consolidation

To investigate the effect of CV-1808 on memory consolidation, we conducted passive avoidance and the Morris water maze tasks using post-acquisition treatment study. CV-1808 (0.25, 0.5, 1, or 2 mg/kg, i.p.) treated immediately after acquisition trial of passive avoidance task or the first training trial of acquisition session of the Morris water maze task did not show any significant effect on the latency time in passive avoidance task and the mean savings in the Morris water maze task compared to the vehicle-treated control group (Fig. 3A and 3B). In addition, CV-1808 did not change the latency time in the acquisition trial in the passive avoidance task (Fig. 3A) and the swimming speed in the Morris water maze task (Fig. 3C).

Effect of CV-1808 on memory retrieval

To investigate the effect of CV-1808 on memory

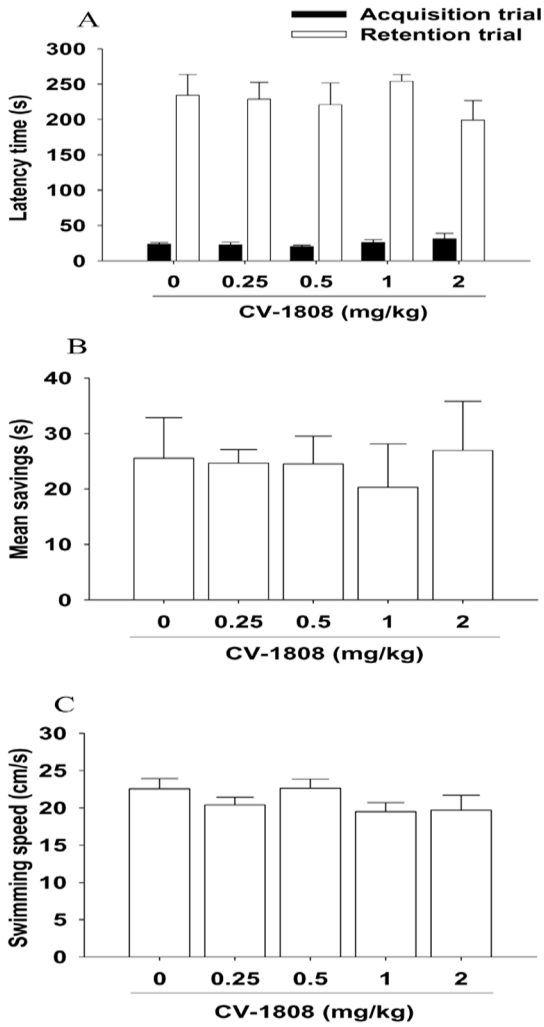

Fig. 3. Effect of CV-1808 (0.25, 0.5, 1, or 2 mg/kg, i.p.) on the consolidation phase of the passive avoidance (A) and Morris water maze tasks (B, mean savings; C, swimming speed). Tasks were evaluated as described in Materials and Methods. Data represent means ± SEM (n = 10/group).

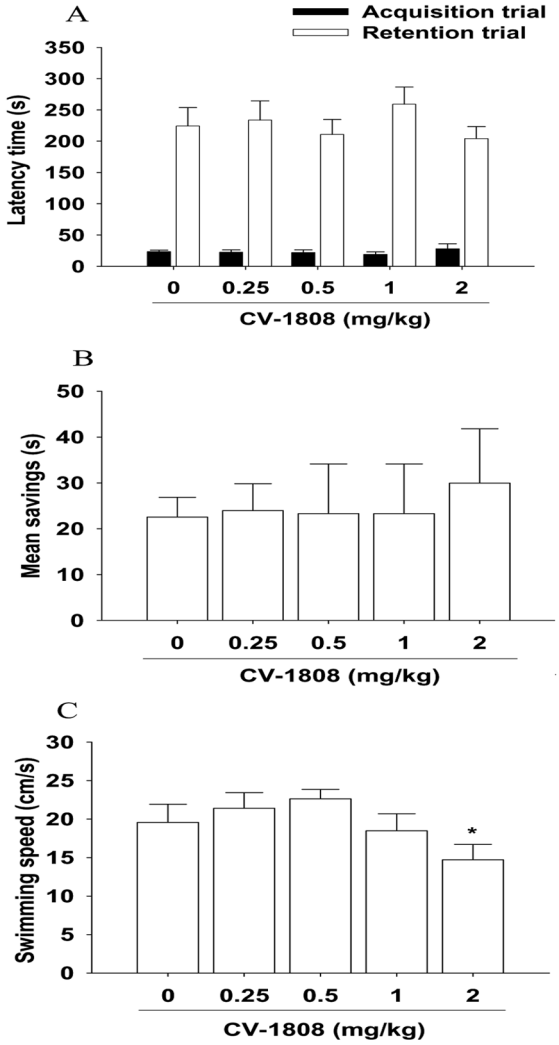

Fig. 4. Effect of CV-1808 (0.25, 0.5, 1, or 2 mg/kg, i.p.) on the retrieval phase of the passive avoidance (A) and Morris water maze tasks (B, mean savings; C, swimming speed). Tasks were evaluated as described in Materials and Methods. Data represent means ± SEM (n = 10/group) (* $P < 0.05$ versus vehicle control group).

retrieval, we conducted passive avoidance and the Morris water maze tasks using pre-retention treatment study. CV-1808 (0.25, 0.5, 1, or 2 mg/kg, i.p.) were treated 30 min before retention trial of passive avoidance task or retrieval session of the Morris water maze task. CV-1808-treated group did not exhibit any significant effects on the latency time in passive avoidance task and the mean savings in the Morris water maze task compared to the vehicle-treated control group (Fig. 4A and 4B). However, in the Morris water maze task, the swimming speed in the CV-1808-treated group (2 mg/kg) was significantly decreased compare with that in the control group ($P < 0.05$, Fig. 4C). These results indicated that acute treatment of CV-1808 (2 mg/kg) deteriorates normal locomotor behaviors.

Discussion

In the present study, we tested the hypothesis that the stimulation of adenosine A_{2A} receptors is likely to have different effects on memory processes. In order to confirm this hypothesis, We conducted pre-, post-acquisition trial, and pre-retention trial treatments of CV-1808 using passive avoidance and the Morris water maze tasks. It was found that the systemic administration of CV-1808

impaired the acquisition phase but not the consolidation or retrieval phases of the learning and memory.

During the passive avoidance task or the Morris water maze task, the acquisitions of an electric shock or of the platform placed are mainly dependent on the hippocampal formation. The existence of A_{2A} receptors in extrastriatal brain regions, such as, the limbic and neocortical areas is now well established (Fredholm *et al.*, 2005), and although they are present in these areas at much lower density than in the striatum (Rebola *et al.,* 2005), the pharmacological activation of hippocampal A_{2A} receptors modulates synaptic transmission and glutamate release (Lopes *et al.,* 2002, Tebano *et al.,* 2005; Diógenes *et al.*, 2004). Recently, the overexpression of A_{2A} receptors was reported to cause deficits in working memory (Giménez-Llort *et al*., 2007), suggesting that the activations of these receptors deteriorates memory performance. Several studies have also demonstrated that adenosine receptor agonists disrupt learning and memory in rats and mice (Normile and Barraco, 1991; Normile *et al*., 1994; Ohno and Watanabe, 1996), and that adenosine receptor antagonists facilitate learning and memory as determined by the passive avoidance task (Nehlig *et al*., 1992, Suzuki *et al*., 1993, Kopf *et al*., 1999; Pereira *et al*., 2002) and another maze task in rodents (Angelucci *et al*., 1999, Hauber and Bareiss, 2001 and Angelucci *et al*., 2002). In the present study, CV-1808 (an adenosine A_{2A} receptor agonist) impaired memory acquisition according to the passive avoidance and Morris water maze tasks. However, it is unclear which receptor site is responsible for cognitive deficits because the roles of presynaptic and postsynaptic adenosine A_{2A} receptors differ. Recently, Rebola *et al*. (2008) reported that the activation of postsynaptic A_{2A} receptor in hippocampal mossy fibers and CA3 pyramidal cells is essentially required for a form of long-term potentiation that occurs via the regulation of NMDA receptor function. The activation of NMDA receptors in CA3 pyramidal cells plays a crucial role in memory acquisition (Kishimoto *et al*., 2006; Nakazawa *et al*., 2002; Rajji *et al*., 2006). Therefore, the observed deterioration of cognitive functions during the acquisition process by CV-1808 is unlikely to be related to the regulation of hippocampal NMDA receptor. Further study is needed to clarify these issues.

Memory consolidation requires gene transcription and de novo protein synthesis, which requires the post-translational modifications of proteins (Silva and Giese, 1994). BDNF expression and activity have been shown to play critical roles in memory formation for various learning tasks (Egan *et al*., 2003; Ou and Gean, 2006; Bekinschtein *et al*., 2007). In addition, although memory consolidation and retrieval processes might involve same synapses, the biochemical changes underlying retrieval are similar but not identical to those underlying consolidation (Barros *et al*., 2003). In the passive avoidance and the Morris water maze tasks, CV-1808 had no effect on the memory consolidation or retrieval phases. To the best of our knowledge, it has not been previously reported that adenosine A_{2A} receptor activation by systemic CV-1808 disrupts memory consolidation. In terms of the retrieval phase, and unlike that found in the present study, Pereira *et al*. (2005) found that stimulation of adenosine A_{2A} receptor by injecting CGS21680 into the posterior cingulate cortex impaired memory retrieval. However, Kopf *et al*. (1999) found that a systemic injection of SCH58261 (an adenosine A_{2A} receptor antagonist) at 180 min after training did not significantly affect passive avoidance task retention. Thus, it appears that the difference between the previous study and ours concerns the use of different injection sites (Pereira *et al*., 2005).

In the present study, we found that CV-1808 (2 mg/kg) reduced swimming speed in the Morris water maze task during the retrieval phase. We also observed that total entry numbers during the Y-maze task were reduced by CV-1808 (2 mg/kg) treatment (data not shown). These findings suggest that the activation of adenosine A_{2A} receptor has a sedative or inhibitory effect on general locomotor behavior. It has been reported that the adenosine A_{2A} agonist, CGS21680, promotes sleep (Satoh *et al*. 1998) and that this sleep promoting effect is mediated by an increase in GABA release, which inhibits the histaminergic systems in rats (Hong *et al*., 2005). This suggests that adenosine A_{2A} receptor plays an important role in the regulation of sleep or locomotor behavior (Ferré S *et al*., 2007). Furthermore, Mingote *et al*. (2008) reported that the systemic administration of CGS21680 (an adenosine A_{2A} agonist) had a sedative effect in rats. Therefore, it is likely that high doses of CV-1808 reduce general locomotor behavior.

In conclusion, our results show that activation of adenosine A_{2A} receptor by CV-1808 detrimentally affects the memory acquisition phase, but not the consolidation or retrieval phase as determined by the passive avoidance and Morris water maze tasks. These results suggest that adenosine A_{2A} receptor is a good target for the development of mnemonic agents.

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