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MCI-225, A Novel Thienopyrimidine Analog, Enhances Attentional Eye Tracking in Midpontine Pretrigeminal Preparation

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EGUCHI, J., Y. SAITOH, M. EGAWA, K.-I. SAITO AND H. KAWAMURA. *MCI-225, a novel thienopyrimidine analog, enhances attentional eye tracking in midpontine pretrigeminal preparation.* PHARMACOL BIOCHEM BEHAV **56**(2) 229–234, 1997.—The effects of MCI-225, a novel psychoactive compound, and reference drugs on attention behavior were studied using visual stimulus induced vertical eye tracking movements in midpontine pretrigeminal (PTG) feline preparation. Surgery was performed under ether anesthesia and subsequently switched to nitrous oxide-fluothane which was discontinued only during experimental sessions. In addition xylocaine was locally injected. Vertical eye movements were monitored by electrooculogram (EOG) and a TV camera. To compare the effects of drugs on eye movement, numbers of spontaneous and tracking eye movements exceeding a present amplitude in EOG were counted before and during the visual stimulation, respectively. MCI-225 (1 and 3 mg/kg, i.v.) enhanced tracking movements dose-dependently without an increase in spontaneous eye movements. No or little change of the electrocorticogram (ECoG) was seen with 1mg/kg MCI-225 and a slight increase in low voltage fast pattern was observed with 3mg/kg, i.v.. On the other hand, tacrine (0.3mg/kg, i.v.), physostigmine (0.03mg/kg, i.v.) and methylphenidate (0.3mg/kg, i.v.) enhanced both types of eye movement and induced ECoG arousal. Desipramine (3mg/kg, i.v.) slightly increased spontaneous eye movement without affecting tracking movements. Piracetam (100mg/kg, i.v.) decreased spontaneous eye movements only. These data clearly show that MCI-225 enhances attention to a moving object and suggest that MCI-225 could be useful in the treatment of attentional deficits and related congnitive dysfunctions in psychiatric disorders. **Copyright © 1997 Elsevier Science Inc.**

MCI-225 Attention Tracking Eye movement PTG preparation

Attentional deficits and abnormal eye movements occur in patients sustaining various kinds of psychiatric disease. For example, in previous reports on senile dementia of the Alzheimer type (SDAT), attention impairment and abnormal eye tracking have been correlated to the severity of dementia (21,29,39). These deficits in both attention and eye tracking have been observed in depressive disorder and also in attention deficit hyperactivity disorders (ADHD) in children (1,7,30).

In general, it is suggested that attention is closely related to the arousal level and either insufficient or excessive arousal levels are inadequate to sustain attention (27). Neurochemically, studies in experimental animals have shown that central noradrenergic neurons play an important role in attention (9,24). Lesions of noradrenergic neurons (NA) produced by the injection of 6 -hydroxydopamine (6-OHDA) into the dorsal noradrenergic bundle (DNB) or by systematic injection of *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4) cause attentional deficits in rodents (25,42). In addition impairments of central cholinergic function are also known to cause attentional deficits in both humans and experimental animals (26,31,32).

In SDAT patients, impairments not only in cholinergic but

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also in noradrenergic neurons have been reported (12,32) and these impairments may be related to attentional deficits. In both depression and ADHD, the hypofunction of the noradrenergic system has been suggested (8,37), and antidepressants, which inhibit the reuptake of NA, are in many cases effective in the treatment of these conditions (18,23). Based on these observations, it appears that catecholaminergic and cholinergic dysfunction in the central nervous system may be involved in these attentional deficits.

MCI-225, a novel thienopyrimidine analog, has been reported to reverse the resistance to extinction in the food rewarded runway response of DNB-lesioned rats (14) and to ameliorate attentional deficit in DSP-4 treated gerbils (42). These results suggest that MCI-225 might enhance attention in these animal models in which the noradrenergic neurons were impaired. Furthermore, MCI-225 reduces learning impairments in basal forebrain-lesioned rats (15), in which attentional deficits with cortical cholinergic dysfunction have been reported (26,31).

Midpontine pretrigeminal (PTG) preparation shows an orientation reflex to visual stimuli and a striking behavioral sign of alertness by vertical eye movements in response to a moving visual stimulus (5), although the transection may damage the locus ceruleus in which the cell body of noradrenergic neurons exist (2). In addition, this preparation keeps relatively long awake electrocorticogram (ECoG) (5) which is needed to perform the task to test attention. From these facts, PTG preparation is thought to be a convenient model to evaluate drug effects on attention.

In this study, we examined the actions of MCI-225 on attentive behavior, tracking eye movements caused by a moving visual stimulus in PTG preparation, in comparison with other psychoactive compounds. To clarify the profiles of these compounds, their effects on spontaneous eye movements and ECoG were also tested.

METHOD

Animals

Useful data were obtained in adult feline of both sexes weighing 2.0–5.7 kg.

Drugs

MCI-225 and piracetam were synthesized and methylphenidate was extracted from Ritalin (Ciba-Geigy) in our laboratory. Tacrine (Janssen), physostigmine (Sigma) and desipramine (Sigma) were purchased commercially. MCI-225 was diluted with 50% propylene glycol and other compounds were diluted in saline. All compounds were administered intravenously.

Surgery

Pretrigeminal transection was performed as described in a previous report (22). In brief, under ether anesthesia, a tracheal cannula was inserted and catheters were placed in the right femoral vein and artery. After craniotomy and aspiration of the cerebellum, the brainstem was transected stereotaxically anterior to the entrance of the trigeminal roots. After transection, respiration was artificially maintained under nitrous oxide-fluothane (70% N_20, 30% 0_2) anesthesia. Both wound margins and pressure points were anesthetized by frequent local injection of xylocaine. Electrooculograms (EOG) were recorded from a silver needle inserted in the lower eye lid and a screw electrode placed on the bony supraorbital arch. ECoGs were recorded with a pair of screw electrodes placed on the frontal cortices. EOG, ECoG and electrocardiogram (ECG) were monitored by a polygraph (Nihon-Kohden). The rectal temperature was maintained at approximately 38°C using a circulating water pad. A black curtain with a small opening through which eye movements were monitored by a TV camera surrounded the preparation to control visual input. The visual stimulus, a white sign (7 × 7 cm) was moved mechanically up and down before the eyes of the preparation and was also hidden behind the black curtain when the moving visual stimulation was not applied.

Procedure

After several hours of recovery time, when the preparation was able to follow a moving stimulus with vertical eye movements, a white sign was moved up and down regularly 10 times per 45 s in every 15 min. After the reproducibility of tracking eye movement was confirmed, a threshold amplitude of EOG was set for each preparation so the 1–3 responses before habituation exceeded the threshold during the visual stimulation in order to compare each drug effect on eye movements. Each compound was injected through the femoral vein cannula immediately after control stimulation and the number of vertical eye movements exceeding a preset amplitude was counted during each stimulation session. In order to examine the drug effects on spontaneous eye movements, the number of spontaneous eye movements for 5 min (between 10 and 15 min after the injection) was also counted.

Statistical analysis

The numbers of the tracking and spontaneous eye movements were analyzed using one-way analysis of variance (ANOVA) followed by Scheffe's test when the F ratio reached significance at the 0.05 level of probability. All data except EOG and ECoG chart were expressed as the mean ± SEM.

RESULTS

Effects on Tracking Eye Movements

Repeated presentation of visual stimulus, a white sign moving up and down 10 times per 45 s, caused habituation in vertical tracking eye movements, a reproducible phenomenon. Figure 1 (left) shows a typical pattern of EOG, when the moving visual stimulus was shown. Injection of 50% propylene glycol did not change either the pattern or amplitude of the EOG during the test period with or without visual stimulation (Fig. 1A). Saline injection did not change tracking eye movements either (data not shown). As shown in Fig. 1B, MCI-225 at 3 mg/kg enhanced tracking eye movements and habituation disappeared. In Figure 1C, a marked increase of both spontaneous and tracking movement is shown after the administration of methylphenidate (0.3 mg/kg, i.v.). Figure 2A. shows the number (see Method) of vertical eye movements during each 45 s visual stimulation period. MCI-225 at 1 and 3 mg/kg induced a dose-dependent increase in the number of vertical eye movements. There were differences in statistical significance among groups at 15 min [$F(3, 23) = 8.0$, $p < 0.01$], 30 min [$F(3, 23) = 3.2$, $p < 0.05$], 60 min [$F(3, 23) = 3.4$, $p < 0.05$] and 75 min [$F(3, 23) = 3.8$, $p < 0.05$] after MCI-225 injection. Animals treated with MCI-225 showed a much higher number vertical eye movements than the vehicle treated group at 15 min ($p < 0.05$) after administration of 1

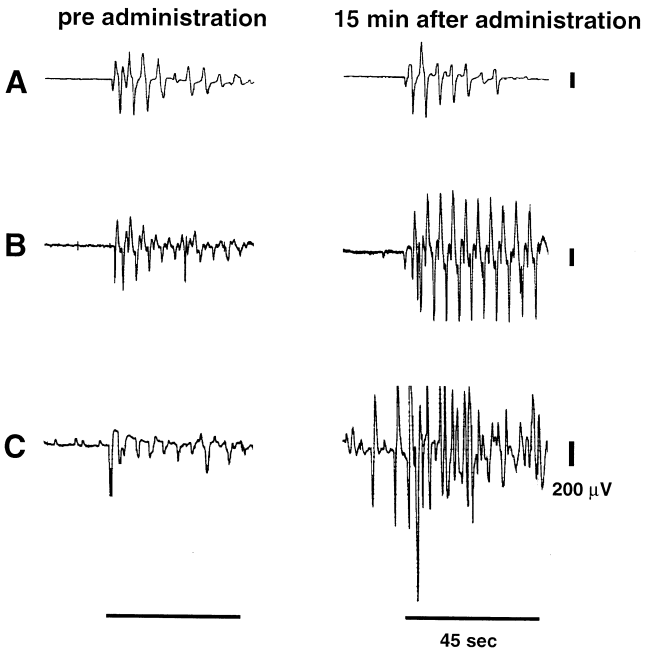

FIG. 1. Effects of i.v. administration of 50% propylene glycol (A), 3 mg/kg MCI-225 (B) and 0.3 mg/kg methylphenidate (C) on the EOG in the PTG preparation. Horizontal bars represent the duration of visual stimulation by a white sign moving up and down 10 times per 45 s sweep. Left: control records before injection, right: records 15 min after injection. Note that methylphenidate enhances vertical eye movements both with and without visual stimulation.

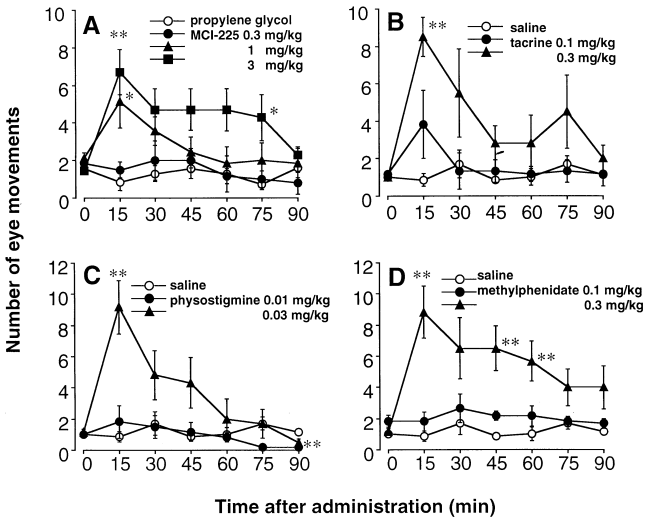

FIG. 2. Effects of i.v. administration of MCI-225 (A), tacrine (B), physostigmine (C) and methylphenidate (D) on the number of vertical eye movements exceeding a certain preset amplitude during visual stimulation. $N = 6$ or 7 per group. $^{*}p < 0.05$, $^{**}p < 0.01$, vs. vehicle treated group (one-way ANOVA followed by Scheffe's test).

mg/kg and at 15 min ($p < 0.01$) and 75 min ($p < 0.05$) after administration of 3 mg/kg. The maximal effects of MCI-225 at both doses were observed at 15 min after administration. All vertical eye movements were confirmed to correspond to the movements of the white sign by a TV camera.

Figure 2B shows the effects of tacrine on the number vertical eye movements. Only at 15 min after administration, was there a significant difference among the three groups [$F(2, 16) = 10.9$, $p < 0.01$] and tacrine (0.3 mg/kg, i.v.) increased the numbers ($p < 0.01$). Figure 2C represents the effects of physostigmine on the number of vertical eye movements. There were significant differences among the groups at 15 min [$F(2, 16) = 16.5$, $p < 0.01$], and 45 min [$F(2, 16) = 4.1$, $p < 0.05$] and 90 min [$F(2, 16) = 8.1, p < 0.05$] after administration. At 15 min after administration, only 0.03 mg/kg physostigmine increased the numbers of eye movements ($p < 0.01$). At 90 min after administration, 0.01 mg/kg physostigmine showed a rather significant decrease in eye movements ($p < 0.01$). The effects of methylphenidate on vertical eye movements and their numbers are shown in Fig. 1C and Fig. 2D, respectively. Methylphenidate at 0.3 mg/kg increased vertical eye movements (Fig. 1C) during visual stimulation. Statistical significances were observed among the groups at 15 min [$F(2, 16) = 19.1, p < 0.01$], 30 min [$F(2, 16) = 3.9, p < 0.05$], 45 min [$F(2, 16) = 13.5, p < 0.01$], 60 min $F(2,16) < 8.5, p < 0.01$] and 90 min [$F(2,16) < 3.7, p < 0.05$]. Only 0.3 mg/kg methylphenidate significantly increased the number at 15, 45 and 60 min ($p < 0.01$). These three compounds changed the pattern of vertical eye movements during visual stimulation at the effective doses. Fifteen minutes after injection of 0.3 mg/kg tacrine, 0.03 mg/kg physostigmine or 0.3 mg/kg methylphenidate (Fig. 1C right), vertical eye movements did not necessarily follow the movement of the white sign and the eyes often moved more than 10 times during visual stimulation.

Desipramine 3 mg/kg and piracetam 100 mg/kg showed no effects on tracking eye movements (data not shown).

Effects on Spontaneous Eye Movements

In order to clarify the profile of each compound, the effects of the drug on spontaneous eye movements were compared. Before drug administration, there was no statistically significant difference in the numbers of spontaneous eye movements for 5 min between 50% propylene glycol and MCI-225 treated groups or between saline and reference drug treated groups. Figure 3 shows the effects of each compound at the maximal doses tested on spontaneous eye movements for 5 min (between 10 and 15 min after drug injection). MCI-225 at 3 mg/kg did not change the number of spontaneous eye movements (see also Fig. 1B, right). Tacrine at 0.3 mg/kg, physostigmine at 0.03mg/kg, methylphenidate at 0.3 mg/kg (see Fig. 1C right) and desipramine at 3 mg/kg, increased the number of spontaneous eye movements to 335%, 277%, 1050% and 204% of the saline-treated group, respectively. Piracetam decreased the number to 15% of the saline treated group.

Effects on ECoG

Figure 4 shows typical ECoGs for PTG preparations treated with the maximal dose of each compound tested. The EGoGs shown were recorded for 5 min before (left) or 10 min after (right) the injection of each compound. Before each injection, ECoG mainly showed an awake or drowsy pattern with some spindle like waves. Injection of 50% propylene glycol, saline or MCI-225 (0.3 and 1mg/kg) caused little change in the ECoG (data not shown). At 3 mg/kg, MCI-225 did not change the ECoG in 5/7 preparations, although there was a slight increase in the occurrence of low voltage fast pattern in the remaining two preparations (Fig. 4A). Tacrine at 0.3

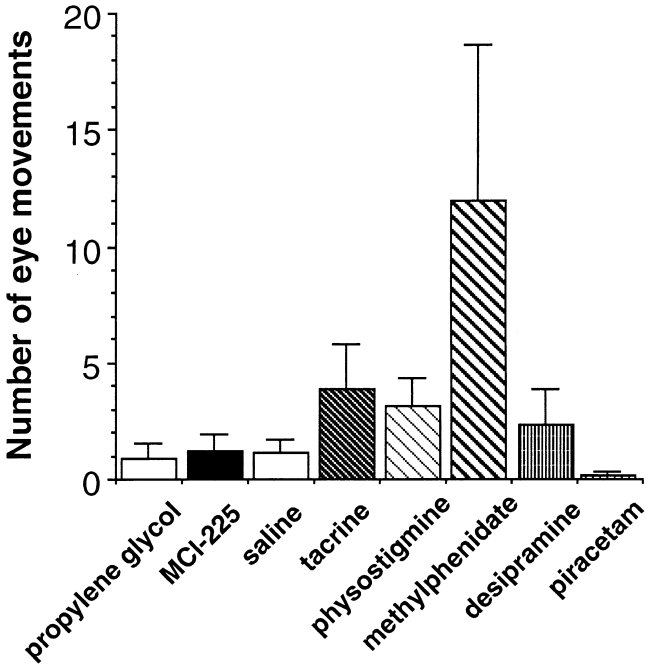

FIG. 3. Effects of i.v. administration of MCI-225 (3 mg/kg), tacrine (0.3 mg/kg), physostigmine (0.03 mg/kg), methylphenidate (0.3 mg/kg), desipramine (3 mg/kg), piracetam (100 mg/kg) and vehicles on the number of spontaneous eye movements exceeding a preset amplitude in the period of 5 min (between 10 and 15 min) after compound administration. $N = 6$ or 7 per group.

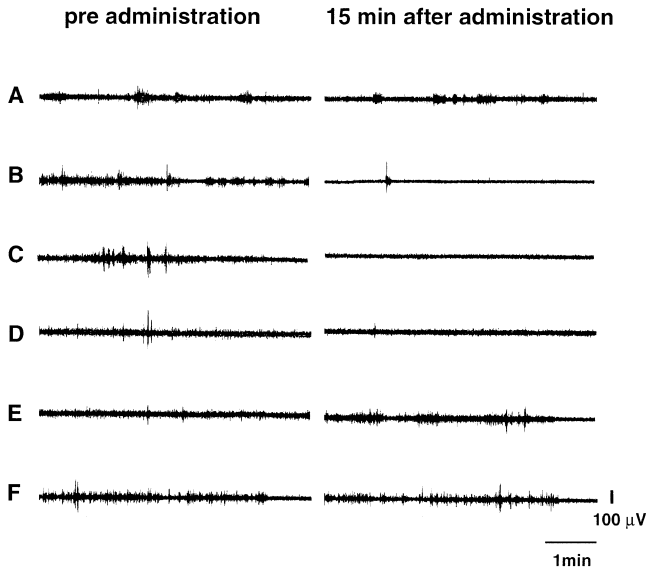

FIG. 4. Typical sample ECoG patterns showing effects of i.v. administration of 3 mg/kg MCI-225 (A), 0.3 mg/kg tacrine (B), 0.03 mg/kg physostigmine (C), 0.3 mg/kg methylphenidate (D), 3 mg/kg desipramine (E) and 100 mg/kg piracetam (F) on the ECoG in PTG preparations. Left: control records before injection, right: records 15 min after injection.

mg/kg (Fig. 4B), physostigmine at 0.03 mg/kg (Fig. 4C) and methylphenidate at 0.3 mg/kg (Fig. 4D) produced an increase in the occurrence of low voltage fast pattern in 3/6, 4/6 and 4/6 preparation tested, respectively. Desipramine at 3 mg/kg (Fig. 4E) increased the spindle like waves in the ECoG in 3/6 preparations and piracetam at 100 mg/kg (Fig. 4F) showed no effects.

DISCUSSION

In PTG preparation, an orientation reflex to novel visual stimuli and habituation of eye tracking after repeated presentation of the moving stimulus occurs. This observation suggests that eye movements following the moving stimulus in this preparation are a response related to visual attention and that this preparation may be a useful model to evaluate the effects of drugs on attention.

In this preparation, MCI-225 at 1 and 3 mg/kg caused a dose-dependent enhancement of tracking eye movements without having any effects on spontaneous eye movements. Therefore, MCI-225-induced enhancement of tracking eye movements is probably not due to a simple excitatory effect on the oculomotor system. Furthermore, since the action of MCI-225 on ECoG was small even at the highest dose tested, the enhancement of tracking eye movements after MCI-225 does not represent a secondary effect caused by a change in the brain either. From these results, it may be concluded that MCI-225 selectively increased responses to moving visual stimuli indicating a possible enhancement of attention in the PTG preparation. On the other hand, 0.3 mg/kg tacrine, 0.03 mg/kg physostigmine and 0.3 mg/kg methylphenidate enhanced not only tracking but also spontaneous eye movements, showing more complicated effects on the oculomotor mechanism. At the effective doses for tracking eye movements, the latter compounds also increased the arousal pattern in the ECoG in more than 50% of the preparations tested, this has been reported in methylphenidate (6) and many cholinomimetic drugs including physostigmine and tacrine (20). Indeed, after injection of these compounds, eye movements were not always sufficiently controlled to track the movements of the white sign. The results with desipramine, which did not enhance tracking eye movements, are rather unexpected, because desipramine ameliorates attentional deficits in rodents with NA depletion (42). In the present study, desipramine at 3 mg/kg, i.v. increased the number of spindle like waves in the ECoG, therefore attention may not be sustained in the PTG preparation under low arousal levels. Desipramine is reported to produce hypnotic effects on the EEG at 4 mg/kg i.m. in cats (19). The present results may be consistent with the arousal level theory of attention that both excessive arousal and insufficient arousal levels are not suitable for sustaining attention (27). MCI-225 may maintain suitable arousal levels for sustaining attention in the PTG preparation. On the other hand, physostigmine, tacrine and methylphenidate may cause excessive arousal while desipramine may cause insufficient arousal.

There appear to be two possibilities concerning the mechanism of action of MCI-225 on the enhancement of tracking eye movements. First, MCI-225 may enhance eye tracking via its action on the central noradrenergic system. As we mentioned before, MCI-225 ameliorates the attentional deficit caused by NA depletion in rodents (14,42). MCI-225 produces a neurochemical enhancement of the central noradrenergic system both pre- and post-synaptically. Namely MCI-225 inhibits the uptake of NA in rat brain synaptosomes (16) and enhances the alpha-potentiation response during cAMP production in rat cortical slices (38,42). Since noradrenergic neu-

rons have been reported to important in attention, and especially in selective attention (10), MCI-225 may enhance attention in the PTG preparation via an enhancement of the noradrenergic neuronal system which might still be alive in such an acute experiment.

A second possibility for the mechanism of MCI-225 is through its action on the 5-HT_3 receptor. MCI-225 potently binds to 5-HT_3 receptors in rat brain (IC50 = 81nM) and inhibits the von Bezold-Jarisch reflex in rats (16). These results suggest that MCI-225 has an antagonistic action on 5-HT_3 receptors in the brain. A selective 5-HT_3 receptor antagonist, ondansetron, is reported to enhance cognitive performance in normal marmosets (13). Since 5-HT_3 receptor antagonists are suggested to enhance the release of acetylcholine from presynaptic terminals in the brain (4), and since the cholinergic neurons are thought to be important not only in memory but also in attention (26,31,33), MCI-225 may enhance attention as a secondary effect on the cholinergic system via 5-HT_3 receptors. To clarify the mechanism of action of MCI-225, further experiments are necessary.

Physostigmine and tacrine may enhance tracking eye movements via their action on the cholinergic system. Based on the minimum effective doses on the number of tracking eye movements, physostigmine appears to be about 10 times more potent than tacrine. Physostigmine is reported to inhibit acetylcholinesterase (AChE) activity and is about 10 times more potent than tacrine (17). These results suggest that these two compounds enhance tracking eye movements mainly via AChE inhibition. The present results showing that both cholinesterase inhibitors did not enhance attention may be interpreted by the hypothesis that tonic postsynaptic stimulation of muscarinic receptors by cholinesterase inhibitors causes hyperactivity in cholinergic systems resulting in an attentional deficit due to hyperattention (36). On the other hand, methylphenidate, which is effective in the treatment of ADHD (11), may enhance tracking eye movements via its actions on both the noradrenergic and dopaminergic systems (35). Since L-3,4-dihydroxyphenylalanine (L-DOPA) enhances spontaneous eye movements in PTG preparation (unpublished data) and dopaminergic agents affect eye movements (3), an increase in spontaneous eye movements induced by methylphenidate may be caused by its actions on dopaminergic neurons. Desipramine is reported to have anti-cholinergic action although it is less potent than imipramine (23,28). This anticholinergic action, which is thought to impair attention (33,36), may have masked its effects on noradrenergic neurons.

In this study, we have demonstrated that MCI-225 selectively enhances tracking eye movements in PTG preparation. This result suggests that MCI-225 could be useful in the treatment of attentional deficits induced by noradrenergic and/or cholinergic dysfunction in psychiatric disorders. In addition the amelioration of attentional deficits could secondarily improve cognitive impairments observed in such disorders (34,40,41), because attentional processes represent critical stages of information processing (36).

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