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Apomorphine-induced hypoattention in rats and reversal of the choice performance impairment by aniracetam

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Abstract

Aging-, disease- and medication-related imbalance of central dopaminergic neurons causes functional impairment of cognition and neuropsychological delirium in humans. We attempted to develop a new delirium model using the direct dopamine agonist, apomorphine, and a choice reaction performance task performed by middle-aged rats. The psychological properties of the model were assessed by determining behavioral measures such as choice reaction time, % correct and % omission. Apomorphine (0.03–0.3 mg/kg s.c.) produced a dose-dependent impairment of task performance. The dose of 0.1 mg/kg prolonged choice reaction time, decreased % correct and increased % omission, indicating that rats had attentional deficits and a reduced arousal or vigilance but no motor deficits or reduced food motivation. This psychological and behavioral impairment of performance resembled that of clinically defined delirium. In this model, the cholinomimetic, aniracetam (10 mg/kg p.o.), reversed the performance impairment induced by apomorphine. Its two metabolites, 2-pyrrolidinone (10 and 30 mg/kg p.o.) and *N*-anisoyl-gamma-aminobutyric acid (GABA, 10 mg/kg p.o.), effectively reversed the performance impairment as the intact drug did. Another pyrrolidinone derivative, nefiracetam (10 and 30 mg/kg p.o.), tended to worsen the apomorphine effect. The cholinesterase inhibitor, tacrine (10 mg/kg p.o.), markedly worsened all of the behavioral measures. Neuroleptics, haloperidol (0.025 mg/kg s.c.), tiapride (30 mg/kg p.o.) and sulpiride (10 and 30 mg/kg p.o.), antagonized the apomorphine effect. The present results suggest that apomorphine-induced behavioral disturbances in the choice reaction performance task seems to be a useful delirium model and aniracetam may improve delirium through the action of 2-pyrrolidinone and *N*-anisoyl-GABA, presumably by facilitating dopamine release in the striatum by acting as an AMPA or metabotropic glutamate receptor agonist.

Keywords: Delirium; Apomorphine model; Choice reaction performance task; Aniracetam; Nefiracetam; Neuroleptic

1. Introduction

Delirium or mental confusion is one of the most common and important psychiatric syndromes in the elderly. The syndrome is clinically associated with attentional impairment, reduction of consciousness and vigilance, global disturbance of cognition, hallucinations, disturbance of the sleep–wake cycles, emotional disturbances and psychomotor disturbance (Lipowski, 1990a). The existence is closely related to dementia, premorbid psychiatric illness and repeated medication, as well as advanced age (Hollister, 1986; Factor et al., 1995) and its occurrence is very high especially in geriatric demented patients after cerebrovascular diseases, such as cerebral infarction and embolism, multiple infarction, transient ischemic attacks and subarachnoid hemorrhage (Lipowski, 1990b).

Some of the commonly noted cognitive dysfunctions of elderly patients may coexist with more fundamental disturbances of attention (vigilance, alertness, awareness, perceptual selectivity, etc.). Dementia is associated with a diminished ability to detect and process stimuli (Foldi et al., 1992), suggesting that it is an attentional disorder in which there is a deficit in an intrinsic attentional function (Sarter, 1994). Both hypo- and hyperattention result in severe cognitive and behavioral dysfunctions (Sarter, 1994) and antedate the disturbances of memory (Broks et al., 1988).

Although the mechanism involved in the induction of delirium is poorly understood, delirium is the clinical expression of neurohumoral disruption and cerebral insufficiency (Crippen, 1994). So, the dysregulation of the

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central nervous system induced by aging, cerebral ischemia or medication is likely to play a major role in the development of delirium. Selective cell loss occurs in certain brain regions, such as the frontal lobes, amygdala, putamen, thalamus, locus coeruleus and cholinergic system, as a result of aging processes (Creasey and Rapoport, 1985). Age-related changes in central neurotransmitter systems (Carlsson, 1985; Simpkins and Millard, 1987) including cholinergic and dopaminergic neurons suggest that older persons are especially prone to this psychiatric disorder (Blass and Plum, 1983).

Diminished function of central cholinergic neurotransmission is thought to be the most likely mechanism of delirium (Francis and Kapoor, 1990), as demonstrated in Alzheimer's disease (Cummings and Benson, 1987). The delirium shown by demented patients is characterized by hypoattention and hypovigilance (Sarter, 1994). Overstimulation of central dopaminergic neurons is considered to cause a psychiatric state associated with hyperattention and hypervigilance, as seen in Schizophrenia, whereas dopaminergic hypoactivity induces attentional dysfunctions in senile dementia (Sarter, 1994) and Parkinson's disease (Robbins and Brown, 1990). The direct dopamine D_1 and D_2 receptor agonist, apomorphine, also produces hallucinations, delusions and confusional states (Factor et al., 1995) and slows down cognitive processing (Ruzicka et al., 1994) in non-demented Parkinsonian patients. These lines of evidence suggest that a disease- and medication-related imbalance in central dopaminergic systems is an important factor that predisposes the patients to the delirious state (Fischer et al., 1990; Factor et al., 1995). The fact that the treatment of choice is neuroleptic medication (Crippen, 1994) emphasizes this still more.

Brain dopamine systems (nigrostriatal and mesolimbic pathways) play a crucial role in a wide variety of behaviors. Dopamine receptor antagonists, neuroleptics, have been shown to attenuate both positively and negatively reinforced operant behaviors at low doses (Fibiger and Phillips, 1979; Wise, 1982). In addition, dopamine depletion in the striatum and nucleus accumbens induces sensorimotor dysfunction and impairs conditioned operant responses (Amalric and Koob, 1987; Robbins and Brown, 1990; Salamone et al., 1991). Thus, it has been proposed that blockade of dopamine transmission disturbs appetitive and aversively motivated behaviors by reducing the 'rewarding impact' of reinforcers such as food, water and electrical stimulation (Wise, 1982; Salamone et al., 1991). Although the underlying mechanism is not understood, it may be involved by deficits in attentive information processing (Robbins and Brown, 1990; Marsden, 1992), motivation (Salamone et al., 1991) and motor ability (Wise, 1982; Amalric and Koob, 1987), deficits which are due to a complex functional difference between the nigrostriatal and mesolimbic pathways. In contrast, dopamine and its agonists are reported to speed up motor performance especially movement initiation, presumably inducing disturbances in time estimation (Ahlenius and Engel, 1972; Baunez et al., 1995).

Nootropic drugs as cognition enhancers are widely used for the treatment of a variety of neuropsychiatric symptoms in patients suffering from cerebrovascular or Alzheimer's disease. Aniracetam is a novel pyrrolidinone derivative and its therapeutic effects on behavioral abnormalities (delirium and nocturnal wandering) and emotional disturbances have been demonstrated in two double-blind studies with patients with cerebral infarction (Otomo et al., 1987, 1991). We have described that the nonselective muscarinic receptor antagonist, scopolamine, causes delirious states (attentional deficits and reduced vigilance), which resemble the clinical symptoms of delirium, in the choice reaction performance task performed by middle-aged rats and that aniracetam improves the performance impairment effectively (Nakamura et al., 1998).

The present study was designed to examine whether apomorphine induces delirious states in rats, based on their ability to perform the two-lever CRP task, and to determine whether aniracetam, which is known to improve these conditions clinically, also has a beneficial effect in this model. For comparison, another pyrrolidinone derivative, nefiracetam, the cholinesterase inhibitor, tacrine and several neuroleptics were evaluated. Three major metabolites of aniracetam were also evaluated to identify the active substance(s).

2. Materials and methods

2.1. Animals

Male Wistar rats aged 8–9 months were obtained from Charles River Japan. Animals were housed in groups of three in a room with a controlled temperature (22 ± 2°C) and relative humidity (55 ± 10%) illuminated from 7.00 a.m. to 7.00 p.m. The diet was restricted so that the animals's weight was maintained at 80% of their free-feeding weight (CRF-1, Charles River Japan).

2.2. Drug preparation and treatment

The drugs used were aniracetam (Ro13-5057, 1-*p*-anisoyl-2-pyrrolidinone: F. Hoffman-La Roche, Basle, Switzerland), *N*-anisoyl-gamma-aminobutyric acid (GABA, Ro13-6680, F. Hoffman-La Roche, Basle), *p*-anisic acid (Tokyo Kasei), 2-pyrrolidinone (Wako), nefiracetam (synthesized in F. Hoffman-La Roche), apomorphine (Sigma), tacrine hydrochloride (tetrahydroaminoacridine: Sigma), tiapride (Sigma), sulpiride (Sigma) and haloperidol (Serenace®: Searle). In the choice reaction performance task experiment, aniracetam, *N*-anisoyl-GABA, *p*-anisic acid, nefiracetam and sulpiride were suspended in 0.25% carboxymethylcellulose solution and apomorphine and haloperidol were dissolved in and diluted

with 0.9% NaCl solution. 2-Pyrrolidinone, tacrine hydrochloride and tiapride were dissolved in deionized water. The rats were injected with apomorphine (0.1 mg/kg s.c.) 25 min prior to behavioral testing, while aniracetam (10, 30 and 100 mg/kg p.o.), tacrine (3 and 10 mg/kg p.o.), haloperidol (0.025 mg/kg s.c.), tiapride (0.3, 3 and 30 mg/kg p.o.) and sulpiride (3, 10 and 30 mg/kg p.o.) were administered 30 min before the apomorphine treatment. All drug solutions were freshly prepared for each experiment.

2.3. Choice reaction performance task

The choice reaction performance apparatus is composed of 14 aluminum/transparent acrylic plate Skinner boxes placed in wooden sound-attenuating compartments. Rats were trained for one to two months prior to the actual experiment, so that they could correctly press the corresponding lever immediately after random presentation of the visual stimulus (cue lamp) above the response lever, as described elsewhere (Nakamura et al., 1998).

Briefly, the beginning of the choice reaction performance task for each trial was signaled by the switching off of the house lamp. Animals were trained to refrain from pressing either of the two levers during the period of differential reinforcement of other behavior (random, 2–5 s). If they repeatedly pressed the levers during the period, the trial was terminated and followed by an intertrial interval (time-out period). During the choice reaction period (maximum 10 s), the time between sample presentation with the cue lamp on and pressing the correct lever was defined as the choice reaction time and a food pellet (reinforcement) was provided through the pellet dispenser. With further lever-pressing responses, the house lamp was switched on and the intertrial interval period (30 s) was begun. One trial took approximately 40 s and a daily session consisted of 30 trials. Training was successfully completed when target parameters for the behavioral measures described below were attained on three consecutive sessions with $>90\%$ correct response, 0.5–2.0 s choice reaction time and fewer than 50 premature responses per session. Thus baseline data were obtained.

The performance and behavioral measures taken were as follows:

Choice reaction time: The latency(s) between the onset of the visual stimulus and the choice/pressing of the correct lever.

% Correct: The proportion of correct responses (pressing a lever signaled by a cue lamp) to total number of responses during the choice reaction period.

% Omission: The proportion of no response to total number of responses during the choice reaction period.

In order to minimize data variation in the experiment for the evaluation of drug efficacy, high responders to apomorphine were selected from the trained animals and non-responders or superhigh responders were excluded. The age of animals was 13–15 months at the beginning of the experiment. The experimental sessions with either test drugs or vehicle were fixed on Tuesdays and Wednesdays. The confirmatory experiments were repeated two or three times ($n = 5$–11 per group in each experiment) and the data were pooled for statistical analysis following confirmation of the results of the first experiment.

2.4. Locomotor activity response

Rats were selected randomly from the group used in the choice reaction performance experiments. Six polycarbonate cages (420W × 260D × 180H) were used on an Actmonitor II (MT Giken, Tokyo) and the spontaneous locomotor activity of an animal was measured by the interruption of an array of electromagnetic waves. Following a 25-min period to habituate the rats to a novel environment, we determined activity at 5-min intervals for 90 min. The animals had no previous experience with this apparatus.

2.5. Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA) followed by a post-hoc multiple comparison

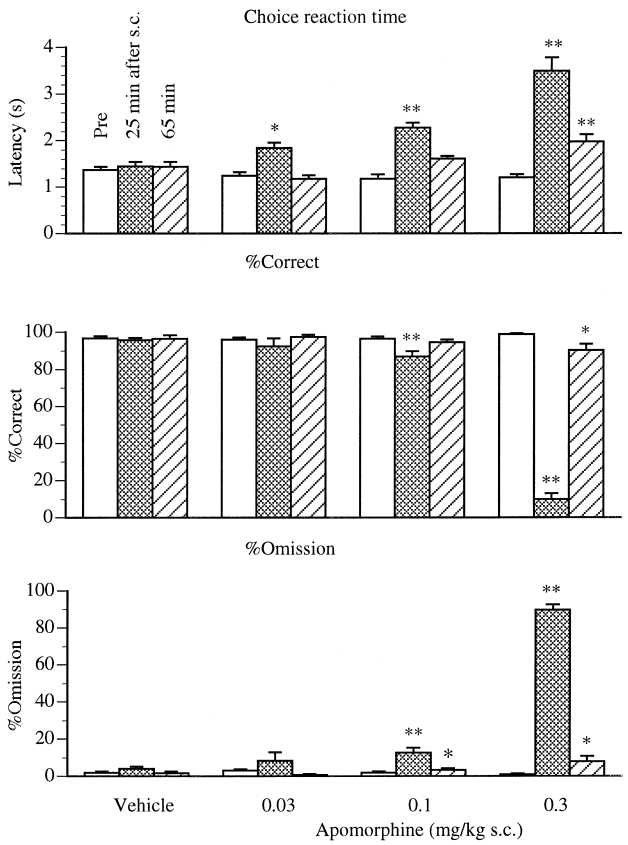

Fig. 1. Effects of apomorphine treatment on the choice reaction performance of rats. Animals in each group ($N = 10$–11) were first subcutaneously injected with vehicle (Pre) and on the next day were injected with either vehicle or apomorphine. Task performance was measured 25 and 65 min after injection. Data represent means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the corresponding Pre value.

using Dunnett's test and a Kruskal–Wallis test followed by a Mann–Whitney's *U* test.

3. Results

3.1. Disturbance of task performance elicited by apomorphine

Apomorphine caused a significant and dose-dependent (0.03, 0.1 and 0.3 mg/kg) prolongation of choice reaction time and reduction in % correct 25 min after its subcutaneous injection, but this negative effect was markedly reduced 65 min after drug injection, though a significant difference was seen with the highest dose. (Fig. 1). The significant increase in % omission was also observed mainly 25 min after dosing. The highest dose had a pronounced effect on each behavioral measure and caused a marked loss of the acquired ability to perform the task. All of these changes were no longer seen 24 h after injection (data not shown). Animals ate up the reward food pellets obtained after the correct response even at the highest dose of apomorphine. Apomorphine dose dependently produced stereotyped behaviors such as licking and sniffing.

3.2. Locomotor change induced by apomorphine

When locomotor activity was examined with the same animals as those used in the choice reaction performance task, apomorphine tended to reduce locomotor activity at 0.03 mg/kg and to increase it at 0.3 mg/kg 25 min after apomorphine injection (Fig. 2). The locomotor change disappeared 65 min later. The locomotor hyperactivity caused restlessness and carelessness in animals and it seems likely that this hyperactivity resulted behaviorally in a parallel and marked decrease in % correct and an increase in choice reaction time and % omission in the choice reaction performance task.

Thus, we decided to evaluate the drug's effect 25 min after the injection of apomorphine at the dose of 0.1 mg/kg in the absence of locomotor change.

3.3. Effects of aniracetam and its major metabolites on apomorphine-induced disturbance of task performance

When aniracetam (10, 30 and 100 mg/kg) was administered orally, the drug at 10 mg/kg produced a significant and maximal increase in % correct and decrease in choice reaction time and % omission compared with the performance of the group treated with apomorphine alone (Fig. 3). The higher doses did not cause a further improvement relative to that seen at 10 mg/kg.

Of the three major metabolites (2-pyrrolidinone, *N*-anisoyl-GABA and *p*-anisic acid) of aniracetam, 2-pyrrolidinone (10 and 30 mg/kg) improved the task performance disrupted by apomorphine (Fig. 4) The metabolite significantly increased % correct and decreased % omission dose dependently and tended to shorten choice reaction time at 30 mg/kg. *N*-Anisoyl-GABA affected the %

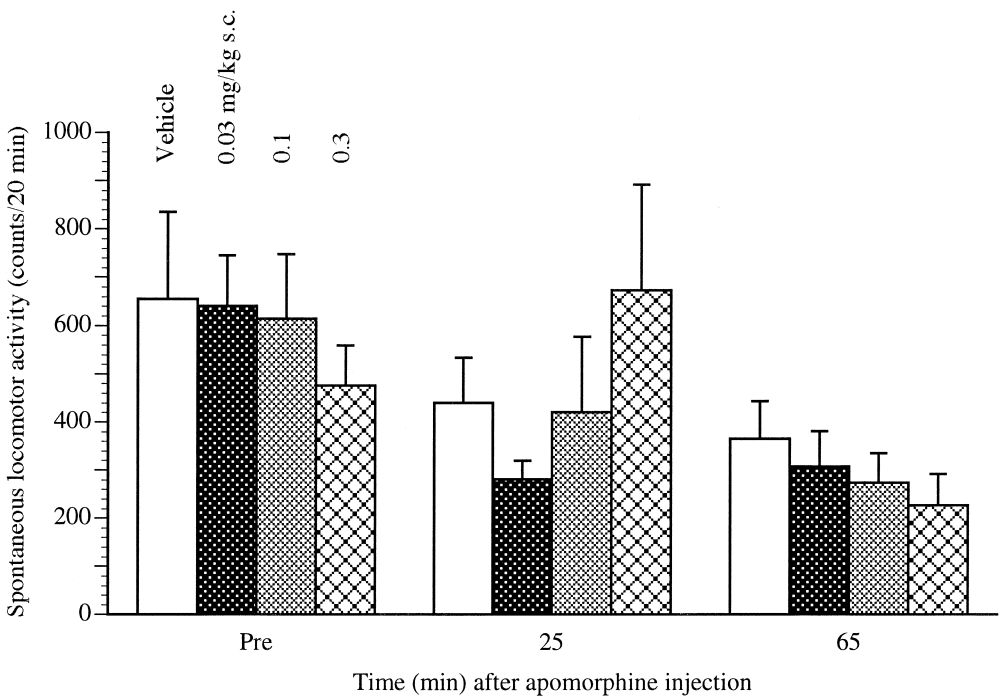

Fig. 2. Effects of apomorphine on the spontaneous locomotor activity of rats. Animals ($N = 6$ per group) were randomly selected from those used in the experiments with the choice reaction performance task. Data represent means ± S.E.M.

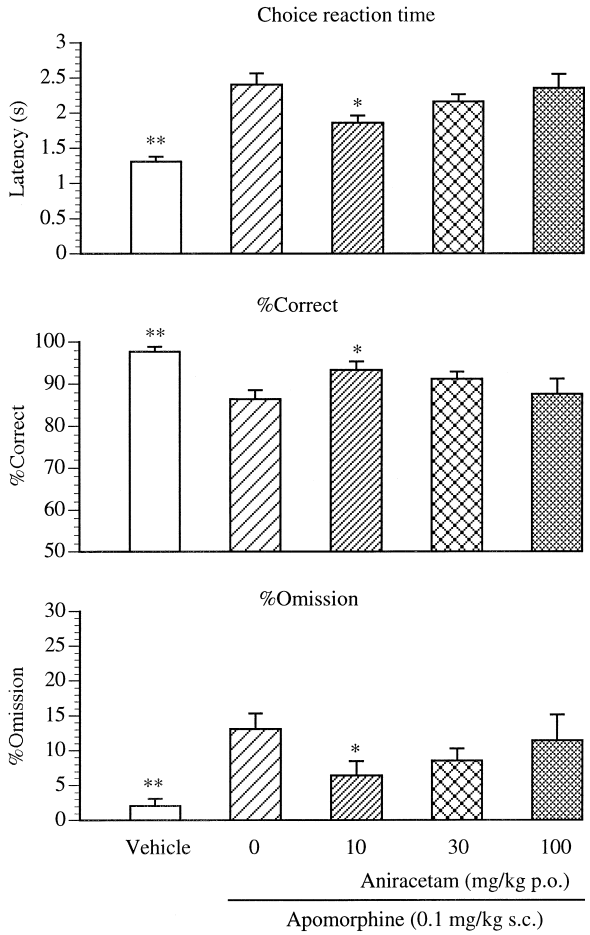

Fig. 3. Effects of aniracetam on the choice reaction performance of rats. Animals ($N = 11–13$ per group) were injected with apomorphine 30 min after the oral administration of aniracetam and a test session was begun 25 min after apomorphine treatment. Data represent means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the group treated with apomorphine alone.

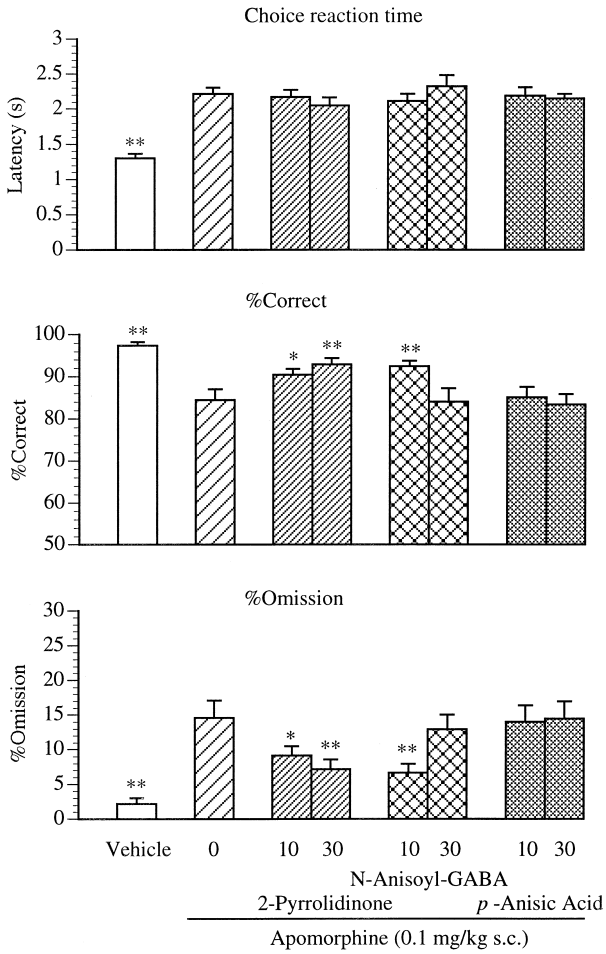

Fig. 4. Effects of 2-pyrrolidinone, *N*-anisoyl-GABA and *p*-anisic acid on the choice reaction performance of rats. Each metabolite (30 mg/kg p.o.) was administered to animals ($N = 13–16$ per group) 30 min prior to the apomorphine treatment. Data represent means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with the group treated with apomorphine alone.

correct and % omission only at 10 mg/kg. The patterns of improvement were consistent with those of aniracetam.

3.4. Effects of nefiracetam and tacrine

Oral administration of nefiracetam (3, 10 and 30 mg/kg) did not significantly affect any behavioral measure (Table 1). As compared with aniracetam, the higher doses of nefiracetam tended to decrease % correct and increase % omission. Thus nefiracetam tended to worsen the behavioral state rather than improve it.

Of the doses of tacrine (3 and 10 mg/kg) used here, the lower dose did not cause improvement, whereas the higher dose produced significant increases in choice reaction time and % omission and a decrease in % correct, probably due to toxic symptoms such as tremor in the tongue in 30% of

Table 1
Effects of nefiracetam on the choice reaction performance task done by rats

Drug	Dose (mg/kg)	Choice reaction time (s)	% Correct	% Omission
Vehicle		1.3 ± 0.1*	96.9 ± 1.0*	2.1 ± 0.7*
Apomorphine	0.1 s.c.	2.1 ± 0.1	89.6 ± 2.0	9.8 ± 2.0
+ Nefiracetam	3 p.o.	2.1 ± 0.2	89.0 ± 2.1	10.2 ± 2.3
+ Nefiracetam	10 p.o.	2.1 ± 0.1	82.6 ± 4.2	16.9 ± 4.3
+ Nefiracetam	30 p.o.	2.1 ± 0.2	83.1 ± 5.6	16.9 ± 5.6

Animals ($N = 13–16$ per group) were injected with apomorphine 30 min after the oral administration of nefiracetam and a test session was begun 25 min after apomorphine treatment. Data represent means ± S.E.M.
* $p < 0.01$ compared with the group treated with apomorphine alone.

Table 2
Effects of tacrine and haloperidol on the choice reaction performance task done by rats

Drug	Dose (mg/kg)	Choice reaction time (s)	% Correct	% Omission
Vehicle		1.3 ± 0.1**	98.3 ± 0.7**	1.5 ± 0.7**
Apomorphine	0.1 s.c.	2.4 ± 0.1	82.7 ± 4.5	17.0 ± 4.5
+Tacrine	3 p.o.	2.6 ± 0.1	83.1 ± 4.4	16.7 ± 4.2
+Tacrine	10 p.o.	3.1 ± 0.4**	38.1 ± 16.9**	61.0 ± 16.6**
+Haloperidol	0.025 s.c.	2.0 ± 0.1*	87.7 ± 3.5	11.8 ± 3.5

Animals ($N = 18–22$ per group) were injected with apomorphine 30 min after the administration of tacrine and haloperidol and a test session was begun 25 min after the treatment. Data represent means ± S.E.M.
* $p < 0.05$.
** $p < 0.01$ compared with the group treated with apomorphine alone.

tested animals, observed 30 min after the administration of 10 mg/kg (Table 2).

3.5. Effects of neuroleptics

A non-sedative and -cataleptic dose of haloperidol (0.025 mg/kg) significantly reversed the choice reaction time prolongation induced by apomorphine and showed a tendency to increase % correct and to decrease % omission (Table 2). Tiapride (0.3, 3 and 30 mg/kg) caused a dose-dependent and significant increase in % correct and a decrease in % omission and shortened choice reaction time at the highest dose (Fig. 5). Sulpiride (10 and 30 mg/kg) significantly improved % correct and % omission and

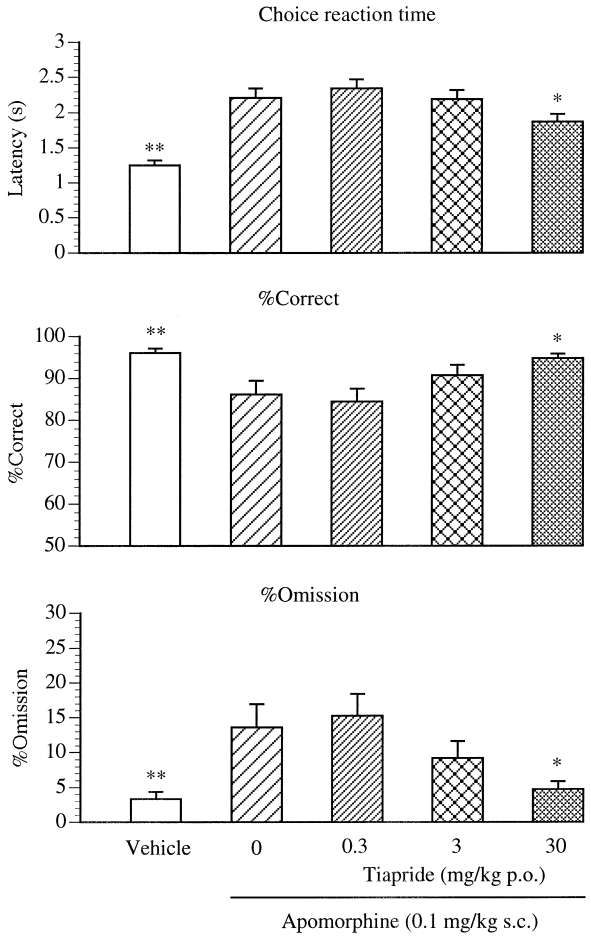

Fig. 5. Effects of tiapride on the choice reaction performance of rats. Animals ($N = 12–14$ per group) were injected with apomorphine 30 min after the oral administration of tiapride and a test session was begun 25 min after apomorphine treatment. Data represent means ± S.E.M. * $P < 0.05$, ** $P < 0.01$ compared with the group treated with apomorphine alone.

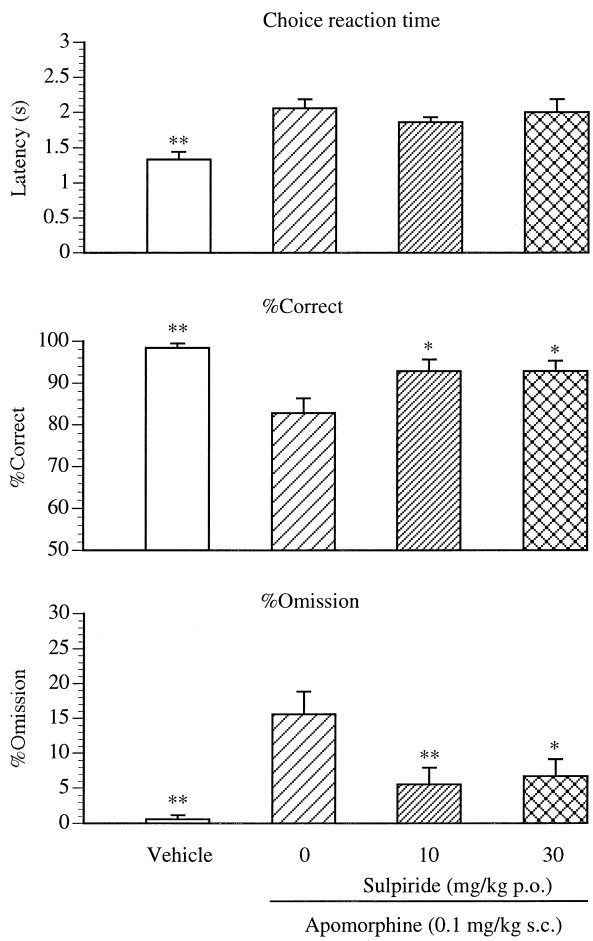

Fig. 6. Effects of sulpiride on the choice reaction performance of rats. Animals ($N = 5–6$ per group) were injected with apomorphine 30 min after the oral administration of sulpiride, and a test session was begun 25 min after apomorphine treatment. Data represent means ± S.E.M. * $P < 0.05$, ** $P < 0.01$ compared with the group treated with apomorphine alone.

tended to shorten choice reaction time at 10 mg/kg (Fig. 6).

4. Discussion

4.1. Apomorphine model of delirium

When administered alone, apomorphine induced a performance impairment which was characterized by a significant and dose-dependent prolongation of choice reaction time, a decrease in % correct and an increase in % omission mainly 25 min after the treatment. The effects of apomorphine on the choice reaction performance task, which were seen reproducibly at 0.1 mg/kg, are summarized in Table 3. The impairment of the task performance seemed to concentrate on choice accuracy and correct response speed and the effects were antagonized by selective dopamine D_2 antagonists such as haloperidol, tiapride and sulpiride.

As described elsewhere (Nakamura et al., 1998), choice reaction time is generally related to decisional processes regarding the correct response to make following the recognition of the visual discriminative stimulus. Since the speed of processing visual information is closely correlated to selective attention (Hikosaka, 1995) and alertness acts on the attention system to enhance the speed of actions taken towards the target (Posner, 1994), the choice reaction time measure is considered to be important for an analysis of selective attention, food motivation or arousal (Carli and Samanin, 1992) as well as motor ability. % Correct is thought to reflect the choice accuracy of task performance requiring sustained attention, especially during the choice reaction period. A reduction of choice accuracy results in a decline in % correct with subsequent attentional disturbance or deficit. % Omission corresponds to an inability to perform the task because of decreased arousal or vigilance and partial motivational dysfunction or motor deficit. Based on these general relationships between behavioral measures, the psychological properties and cognitive functions, apomorphine at 0.1 mg/kg was thought to disrupt attentional function (selective and sustained) and arousal or vigilance without affecting locomotor activity or food motivation. The change in each behavioral measure was consistent with those obtained for the selective dopamine D_2 antagonist, raclopride, by Baunez et al. (1995).

Table 3
Summary of the effect of test drugs on performance of the choice reaction task by rats

Drug	Choice reaction time	% Correct	% Omission
Apomorphine	▲	▼	▲
Aniracetam	⇓	⇑	⇓
2-Pyrrolidinone	↓	⇑	⇓
N-Anisoyl-GABA		⇑	⇓
p-Anisic acid			
Nefiracetam		↓	↑
Tacrine	⇑	⇓	⇑
Haloperidol	⇓	↑	↓
Tiapride	⇓	⇑	⇓
Sulpiride	↓	⇑	⇓

▲ or ▼: A significant ($P < 0.05$) increase or decrease by apomorphine.
⇑ or ⇓: A significant ($P < 0.05$) increase or decrease by each drug against apomorphine-induced change.
↑ or ↓: A tendency to increase or decrease.

4.2. Underlying mechanism

Apomorphine is generally considered to preferentially stimulate pre and/or postsynaptic autoreceptors in central dopaminergic pathways (Roth, 1979). It is well known that the postsynaptic activation of dopaminergic neurons induces dopaminergic psychosis (including delirium) in animals, as demonstrated by the impairments in the water finding task elicited by a high-dose of apomorphine (Nabeshima et al., 1994) and in the passive avoidance task elicited by ketamine (Uchihashi et al., 1994) and by the increased number of incorrect lever pressings in the choice reaction performance task elicited by methamphetamine (Himori and Mishima, 1994), and in Schizophrenic patients and medication-treated Parkinsonian patients (Sarter, 1994; Factor et al., 1995).

Apomorphine systemically injected at low doses has been reported to lower striatal dialysate dopamine concentrations in conscious rats (Imperato et al., 1988; Kuczenski et al., 1990) and to inhibit nerve terminal dopamine synthesis (Zigmond et al., 1989; Tissari and Lillgals, 1993). Consistent with these neurochemical findings, the drug reduces spontaneous locomotion activity (Strömbom, 1976; Kuczenski et al., 1990) and amphetamine-induced motor activity (Kuczenski et al., 1990) and ameliorates the ketamine-induced disruption of passive avoidance learning (Uchihashi et al., 1994). Taken together, these results indicate that low-dose apomorphine inhibits dopaminergic nerve impulse flow, possibly via the activation of mainly presynaptic dopamine autoreceptors (Roth, 1979; Skirboll et al., 1979) and elicits attentional dysfunctions as observed in this study.

Furthermore, there is evidence that dopamine receptor antagonists and drug-induced dopamine depletion impair the performance of various conditioned motor tasks. For example, selective blockade of dopamine D_2 receptors by raclopride at noncataleptic doses disturbed accuracy and speed in a reaction-time task performed by rats, whereas selective blockade of dopamine D_1 receptors did not (Amalric et al., 1993; Marrow et al., 1993; Baunez et al., 1995). The change in performance closely resembled the deficits induced by the mixed dopamine D_1/D_2 receptor

antagonist, α-flupenthixol (Amalric and Koob, 1987). Haloperidol at low doses has been shown to disrupt operant tasks in animals such as the lever-pressing response (Salamone et al., 1991) and lever release response (Marrow et al., 1993) for food. In addition, dopamine depletion in the corpus striatum but not in the nucleus accumbens impairs the lever release response in the sensitive reaction time task (Amalric and Koob, 1987). The release and metabolism of dopamine in the striatum or nucleus accumbens is elevated during lever-pressing for food (Church et al., 1987; Salamone et al., 1989) and most of the striatal neurons increase the firing rate during the execution of motor tasks (Ljungberg et al., 1992; Wang and Rebec, 1993), findings which they appear to paradoxically support the above data. Haloperidol also worsens the residual cognitive abilities of demented patients (Devanand et al., 1989).

The nigrostriatal dopaminergic system is thought to play a crucial role in the initiation and the sequencing of conditioned motor acts (Iversen, 1977) and in the control of performance in a motor task requiring a higher level of information processing (Robbins and Brown, 1990). Indeed, striatal dopamine depletion induces attentional (Robbins and Brown, 1990) and motor initiation (Amalric and Koob, 1987) deficits in rats. However, apomorphine did not clearly affect the number of premature response (the number of the lever pressings in the periods of differential reinforcement of other behavior and intertrial interval) in the present study (data not shown). This suggests that apomorphine at a low dose does not induce motor initiation deficits, since this behavioral measure is thought to be a better index of time estimation (Baunez et al., 1995). Thus, low-dose apomorphine acts on dopamine D_2 autoreceptors preferentially and impairs appetitively reinforced operant responses in middle-aged rats, which presumably reflect hypoattention and hypovigilance caused by dopaminergic dysfunction in the striatum. This behavior seemed to resemble that seen in delirium.

4.3. Biphasic locomotor change

The performance impairment induced by apomorphine was accompanied by a tendency to hypoactivity at 0.03 mg/kg and to hyperactivity at 0.3 mg/kg and with dose-related stereotyped behaviors. It is suggested that dopamine D_1 receptors in the nucleus accumbens, which are mainly involved in locomotor hyperactivity and positive reinforcement (rewarding), are activated by psychomotor stimulants such as cocaine and amphetamine (Koob et al., 1987; Cabib et al., 1991; Hiroi and White, 1991; Le Moal and Simon, 1991). The following may provide a possible explanation for the biphasic change in locomotor activity. The lowest dose of apomorphine could preferentially stimulate dopamine autoreceptors (Roth, 1979; Skirboll et al., 1979) in the mesolimbic dopaminergic system and results in a decrease in locomotor activity, as shown by others (Strömbom, 1976; Kuczenski et al., 1990). In addition, dopamine depletion in the nucleus accumbens reduces spontaneous and amphetamine-induced locomotor activity (Kelly et al., 1975). In contrast, the highest dose could enhance dopamine transmission largely through direct stimulation of postsynaptic dopamine D_1 receptors and causes locomotor hyperactivity (Roth, 1979; Strömbom, 1976). The middle dose appears to sustain a stimulatory balance between presynaptic dopamine D_2 autoreceptors and postsynaptic dopamine D_1 and D_2 receptors, which mimics normal neuronal activity in the mesolimbic dopaminergic pathway. These data and our findings indicate that the apomorphine-induced performance impairment is independent of locomotional change, and thus the nucleus accumbens may not be actively involved in the apomorphine effect. We have reported that the choice reaction time measure in the choice reaction performance task is almost unaffected by the locomotor activation elicited by scopolamine (Nakamura et al., 1998).

Based on the above-mentioned data, it would appear that the disturbance of task performance induced by apomorphine resembles delirium in patients with dementia or medication-induced psychiatric symptoms, both behaviorally and psychologically. Hence, the apomorphine model of delirium may prove to be useful for evaluating nootropics and antipsychotics.

4.4. Improvement by aniracetam

As summarized in Table 3, aniracetam like its metabolites, 2-pyrrolidinone and *N*-anisoyl-GABA, significantly improved the choice reaction time, % correct and % omission disrupted by apomorphine. The aniracetam effects were similar to those seen previously in different animal models such as ischemic-hypoxic rats (Himori and Mishima, 1994), aged rats (Kubota et al., 1986a), stroke-prone spontaneously hypertensive rats (Kubota et al., 1986b) and scopolamine-treated middle-aged rats (Nakamura et al., 1998). The reduction of % omission by aniracetam was not due to its action on motor function, as judged by the fact that the drug did not produce any change in general behavior when administered alone to animals at doses higher than the ones used in this experiment (Himori et al., 1986). The vigilance-enhancing effects of aniracetam have been demonstrated by the spectral analysis of electroencephalograms recorded from rats (Santucci et al., 1989) and monkeys (Schwam et al., 1985), as well as from geriatric subjects (Saletu et al., 1980). These results suggest that aniracetam may increase arousal or vigilance, so that rats 'concentrate' on task performance, and consequently improve their choice accuracy and response speed. Pietrusiak et al. (1986) found that aniracetam significantly attenuated the distal cue deficits of mice performing a water maze task, indicating the reversing effect of aniracetam on attentional deficits.

Several kinds of glutamate subtype receptors are found in the striatum (Nakanishi and Masu, 1994), which receives glutaminergic afferent input from the cortex (Perschak and Cuénod, 1990). Excitatory amino acids including α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) facilitate dopamine release from the striatum in vitro (Clow and Jhamandas, 1988) and in vivo (Barbeito et al., 1990; Imperato et al., 1990). More recently, it has been reported that intrastriatal injections of AMPA and of the metabotropic glutamate receptor agonist, *trans*-(1*S*, 3*R*)-1-amino-1,3-cyclopentanedicarboxylic acid (*trans*-ACPD), elicit contralateral turning in intact rats; this turning behavior can then be blocked with dopamine receptor antagonists (Sacaan et al., 1992; Smith and Beninger, 1996; Smith et al., 1996). These authors suggested that AMPA- and *trans*-ACPD-induced turning behavior depends on the stimulation of postsynaptic dopamine receptors by dopamine released presynaptically. Similarly, GABA type A receptor antagonists cause contralateral turning (McKenzie et al., 1991) and elevate striatal discharge, as do glutamate receptor agonists (Herrling, 1985). Zivkovic et al. (1995) found that aniracetam improved the disruption of water maze performance produced by the full allosteric modulator of $GABA_A$ receptors, alprazolam, by acting as a positive allosteric modulator of ionotropic AMPA receptors (Martin and Haefely, 1993) and inhibiting GABA transmission. Fallarino et al. (1995) suggested that aniracetam binds to its recognition site within the AMPA receptor complex. Therefore, it seems likely that aniracetam as an AMPA or metabotropic (Pizzi et al., 1993, 1996) glutamate receptor agonist may release dopamine in the striatum through an indirect mechanism, thereby enhancing striatal glutaminergic transmission, inhibiting striatonigral GABAergic projection (Smith et al., 1996) and antagonizing the apomorphine effect. Indeed, the single oral administration of aniracetam reduced striatal dopamine content in rats (Petkov et al., 1984). This may explain the clear difference in the improvement of the apomorphine-induced disturbance by aniracetam and nefiracetam, despite the fact that both pyrrolidinones commonly facilitate cholinergic transmission (Kawajiri et al., 1990; Watabe et al., 1990; Martin and Haefely, 1993). It suggests that the reversing effect of aniracetam is not mediated by cholinergic activation. Moreover, nefiracetam might potentiate the effect of apomorphine by facilitating GABAergic neuronal transmission (Watabe et al., 1993; Nabeshima et al., 1994).

The bell- or U-shaped dose–response curve for the above measures appears to be related to the state of arousal of the animals (Steckler et al., 1994). Both hypoactivity elicited by apomorphine and hyperactivity elicited by aniracetam of the striatal dopaminergic system are equally likely to worsen task performance. Increasing doses of aniracetam may gradually change the state of arousal of the rats, from underarousal (hypoattentive) after apomorphine alone to overarousal (hyperattentive). Consequently, overaroused animals would no longer benefit from further stimulation.

Our findings support the clinical efficacy of aniracetam experimentally. Otomo et al. (1987, 1991) reported that aniracetam markedly improved delirium as well as nocturnal wandering in patients with cerebral infarction. In addition, the oral administration of aniracetam reversed cognitive deficits in psychometric tests performed by elderly subjects (Saletu et al., 1980) and by hypoxic young healthy subjects (Saletu and Grünberger, 1983). It also improved the performance of memory and information processing tasks by young healthy volunteers injected with scopolamine (Wesnes et al., 1990) and the performance of simple reaction time and neuropsychological tasks by elderly patients with senile dementia of the Alzheimer's type (Senin et al., 1993). Together, most of these clinical results indicate that the therapeutic effects of aniracetam involve an improvement in cognition and visual information processing and lengthen the attention span.

4.5. Other drugs

Contrary to our expectations, tacrine did not improve performance of the choice reaction performance task disrupted by apomorphine, again indicating that the improvement elicited by aniracetam is independent of cholinergic activation. Conversely, tacrine at the higher dose worsened all measures, probably due to its nonselective properties.

Since sedation affects the performance of the choice reaction performance task, we used non-sedative and non-cataleptic doses of haloperidol in the present study. Haloperidol as well as tiapride and sulpiride improved task performance as a whole without affecting motor function, indicating that the apomorphine-induced delirious state is primarily mediated by dopamine D_2 receptors. The fact that these neuroleptics, which are used to treat delirium clinically, were effective in the present study emphasizes the usefulness of apomorphine-induced choice performance impairment as a model of delirium.

In conclusion, we show here that apomorphine at a low dose causes attentional deficits and a reduction of arousal or vigilance in the choice reaction performance task performed by middle-aged rats, as shown by the changes in choice accuracy, choice latency and choice omission. These changes seems to be mainly mediated by striatal dopamine D_2 receptors and are related to the delirium seen in senile dementia and Parkinson's disease, both behaviorally and psychologically. The nootropic drug, aniracetam, effectively reversed the apomorphine-induced delirious state, as already demonstrated clinically in the treatment of demented patients after cerebral stroke. The improvement elicited by aniracetam may be due to a facilitation of dopamine release in the striatum by its action as an AMPA or metabotropic glutamate receptor agonist and by the action of its two major metabolites, 2-pyrrolidinone and *N*-anisoyl-GABA. These observations strongly suggest the

involvement of the central dopaminergic system in delirium.

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