ELSEVIER

Pharmacology, Biochemistry and Behavior 68 (2001) 65–69

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Aniracetam restores motivation reduced by satiation in a choice reaction task in aged rats

Kazuo Nakamura*, Mitsue Kurasawa

CNS Supporting Laboratory, Nippon Roche Research Center, 200 Kajiwara, Kamakura, Kanagawa 247-8530, Japan

Received 9 November 1999; received in revised form 31 July 2000; accepted 4 September 2000

Abstract

This study aims to examine the effects of aniracetam on satiation-induced poor performance in a choice reaction task. Aged rats that mastered the task under food restriction stably maintained the task performance for a long period. Satiation by successive free feeding greatly diminished the performance. Satiation resulted in a decreased % correct, increased % omission and prolonged choice reaction time, indicating a reduction in lever response with low choice accuracy and slow responding speed. Repeated administration of aniracetam (30 mg/kg, po, for 14 days) partially recovered the choice accuracy and lever response, but not the responding speed, task-associated motor activity or impulsivity. In addition, aniracetam did not affect the animals' weights. These results indicate that satiation reduces motivation to perform and attain the task. Aniracetam may restore motivation, probably by improving poor behavioral states (daily attentional and vigilance failures), thereby creating the driving force.

Keywords: Aniracetam; Choice reaction task; Satiation; Motivation; Attention and vigilance; Aged rats

A reduction in motivation and spontaneity as a consequence of cerebrovascular diseases interferes with rehabilitation of the physical impairment, disability and handicaps caused by neurological factors (hemiplegia and hemiparesis). Consequently, activities of daily living (ADL) in these patients are depressed and the quality of life is reduced. As compared with other inhibitory factors such as delirium, depression, dementia and mental shock, spontaneity has been reported to most strongly affect ADL in elderly stroke patients (Katayama, 1998). Therefore, effective rehabilitation therapy of stroke greatly depends on each patient's motivation and cognitive ability (perceptions) (Schut, 1988; Vanetzian, 1997). Poststroke depression is also suggested to lower physical functional ability by increasing fatigue and feelings of hopelessness, while decreasing motivation (Schubert et al., 1992). To improve ADL, therapeutic drugs that treat mental impairments (i.e., decreased spontaneity/motivation, disrupted consciousness and depression) are required.

Aniracetam, a cognition enhancer, is used clinically to treat emotional disturbances (anxiety, agitation and depressed mood), sleep disorders and behavior problems (nocturnal delirium, wandering) that are associated with cerebral infarction (Katsunuma et al., 1998; Otomo et al., 1991) and Alzheimer's and Parkinson's diseases (Honma et al., 1995; Katsunuma et al., 1998; Senin et al., 1993). Interestingly, the compound is particularly effective for poststroke depression accompanied with both sleep disorders and anorexia (Kurosu et al., 1998). Aniracetam has been shown to possess mechanisms for positively modulating cholinergic and glutaminergic nervous systems, as well as increasing synaptic efficacy and energy metabolism (Himori et al., 1992; Martin and Haefely, 1993; Pizzi et al., 1993). The clinical effectiveness of aniracetam has been demonstrated in relation to behavioral and psychiatric symptoms and syndromes, such as hallucination, attention deficits, low vigilance, anxiety, impulsivity, depression, temporal dysregulation and sleep abnormality, in animals (Kimura et al., 2000; Kurasawa et al., 2000; Nakamura and Kurasawa, 2000; Nakamura et al., 1998a,b, 2000; Tanaka et al., 1998, 2000). However, there has been no experimental study to support its therapeutic efficacy on spontaneity or motivation.

* Corresponding author. Tel.: +81-467-47-2228; fax: +81-467-47-2219.

E-mail address: kazuo.nakamura@roche.com (K. Nakamura).

0091-3057/01/$ – see front matter
PII: S0091-3057(00)00440-8

It is, therefore, noteworthy to study the effects of aniracetam on disruption of food-motivated operant behavior or a progressive decline of daily task performance as an index of motivation. The present study investigates the drive to perform an attention and vigilance task (two-lever choice reaction), and to augment the clinical usefulness of aniracetam by examining its effects on motivation. Aged rats were used because food restriction or fasting seriously affects an adaptive behavioral function in young rats and thereby markedly lowers circadian motor activity (especially diurnal activity) (Tanaka et al., 2000). Additionally, most of the patients treated with aniracetam are elderly and geriatric.

1. Method

1.1. Animals

Male Wistar rats (8–9 months of age) were obtained from Charles River Japan. They were housed in groups of three and maintained in a room with controlled temperature (22 ± 2°C) and relative humidity (55 ± 10%). The room was illuminated from 07:00 to 19:00 hours. Access to diet (CRF-1, Charles River Japan) was restricted so that animals' weights were maintained at 80% of their free-feeding weight, in order to motivate the lever-pressing behavior for food reinforcement. The study was carefully performed in accordance with guidelines (Principles of Laboratory Animal Care) dictated by the Animal Care and Use Committee of Nippon Roche Research Center and approved by the Japanese authorities.

1.2. Choice reaction task

The choice reaction apparatus consisted of 14 two-lever operant conditioning chambers (Skinner boxes) enclosed in wooden, sound-attenuating compartments. The basic equipment and interface-controller system are detailed elsewhere (Nakamura et al., 1998a).

Briefly, rats were trained daily (Monday through Friday) for 1–2 months from the age of 9–10 months. They were allowed to press the appropriate lever with a continuous schedule of a fixed ratio 1, immediately after presentation of a visual stimulus (cue lamp) above the response lever. The session onset was indicated by switching off the house light. Animals were trained to refrain from pressing either of the two levers for a random period (2–5 s) of differential reinforcement of other behavior (DRO). A lever press during the DRO period repeatedly reset the DRO within 10 s. During the choice reaction period (5–8 s), the time between the cue lamp activation and the correct response was defined as the choice reaction time (CRT). A correct response delivered a single food pellet (45 mg, Bioserv, NJ, USA) as a positive reinforcer. Pressing the wrong lever was counted as an incorrect response. The cue lamp remained illuminated until the rats pressed either the correct or incorrect lever during the choice reaction period. Following the choice reaction period, the house light was switched on and an intertrial interval (ITI) period (time-out period for 30 s) began. Each test session consisted of 30 trials, lasting approximately 40 s each. Training was considered successful when the following criteria for the behavioral measures were attained in three consecutive sessions: greater than 90% correct response, 0.5–2.0 s CRT as an average of the 30 trials and fewer than 50 premature responses (the total number of lever responses during the both periods of DRO and ITI per session). The performance and behavioral measures are summarized as follows: % correct — the percentage of correct responses performed during the choice reaction periods; % omission — the percentage of null responses during the choice reaction periods; and CRT — the average latency between the onset of the cue lamp and the correct lever response.

The animals that were successful at the choice reaction task were retrained to repeat the task during aging. The long-term repetition of the task performance, which was always conducted on Tuesdays and Wednesdays, lasted for 13–14 months under dietary restriction. At approximately 26 months of age, the rats were changed from restricted feeding to free feeding, and the effects of satiety on food-motivated behavior were monitored for 64 days. Following this period, aniracetam or vehicle was orally administered to the rats once daily for 14 consecutive days. Rats were allowed free access to food during the treatment.

1.3. Drugs

Aniracetam (Ro13-5057; synthesized in F. Hoffman-La Roche, Basle, Switzerland) was suspended in 0.25% carboxymethyl cellulose solution containing one to two drops of Tween 80. A test session to evaluate the effects of aniracetam was begun 1 h after the last dosage.

1.4. Task-associated motor activity

Motor activity related to the performance of the choice reaction task was measured with the AB system (Neuroscience, Tokyo, Japan). A sensor located on the ceiling of the box recorded infrared beam breaks as the rat moved in the test chamber.

1.5. Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's *t* test and paired data were analyzed by Wilcoxon signed-rank test. Repeatedly measured data were analyzed by repeated measures one-way ANOVA followed by multiple comparison of Ryan–Einot–

Gabriel–Welsch test. A P value of less than .05 was considered statistically significant.

2. Results

Following acceptable performance in the choice reaction task, the same animals were later tested to examine age-related effects in the choice reaction task. The task performance proved stable over time (13–14 months) as assessed by % correct (accuracy: 90.4–99.0%) and CRT (responding speed: 1.32–1.60 s) (Fig. 1). Throughout the study, animals displayed no age-related reduction in choice accuracy or CRT. Moreover, isolation from the choice reaction task for several months did not alter the subsequent task performance (Fig. 1).

At the age of 26 months, dietary restriction was replaced with free feeding in an effort to reduce the motivation of food-restricted rats. The motivational deficits after free feeding occurred rapidly and significantly affected food-motivated task performance. Percent omission dramatically increased from 0.95% to 38.5% [$F(5,89)=10.5$, $P<.01$] by free feeding for 64 days. Percent correct rapidly decreased from 97.1% to 73.5% [$F(5,89)=12.3$, $P<.01$] within the first 7 days and the CRT was extended from 1.51 s to 2.12 s [$F(5,89)=5.69$, $P<.01$] (Fig. 1). Percent correct and CRT performance decayed over time and reached plateau levels (57.5% for % correct and 2.38 s for CRT, $P<.01$) 64 days after the onset of free feeding. Total lever responses (mainly correct plus premature responses) were only reduced by 20% through free feeding. Animals' body weights significantly increased by about 40% ($P<.001$) (Fig. 3).

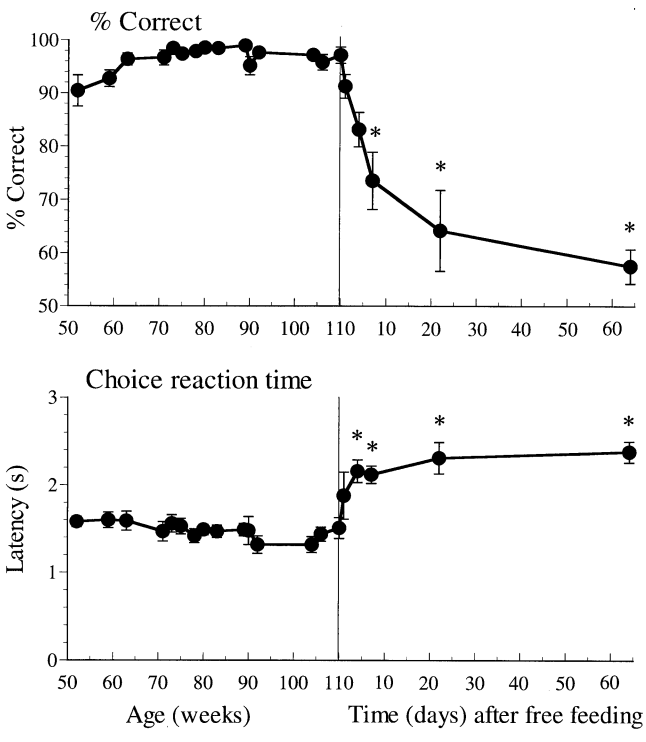

Fig. 1. Daily task performance during aging and the decline after free feeding. Well-trained rats were subjected to the choice reaction task for a long period (16 months) while food restricted and then allowed to free-feed for 64 days. Data show means ± S.E. ($n=19$). * $P<.01$, compared with pre-free feeding (repeated-measures one-way ANOVA followed by Ryan–Einot–Gabriel–Welsch test).

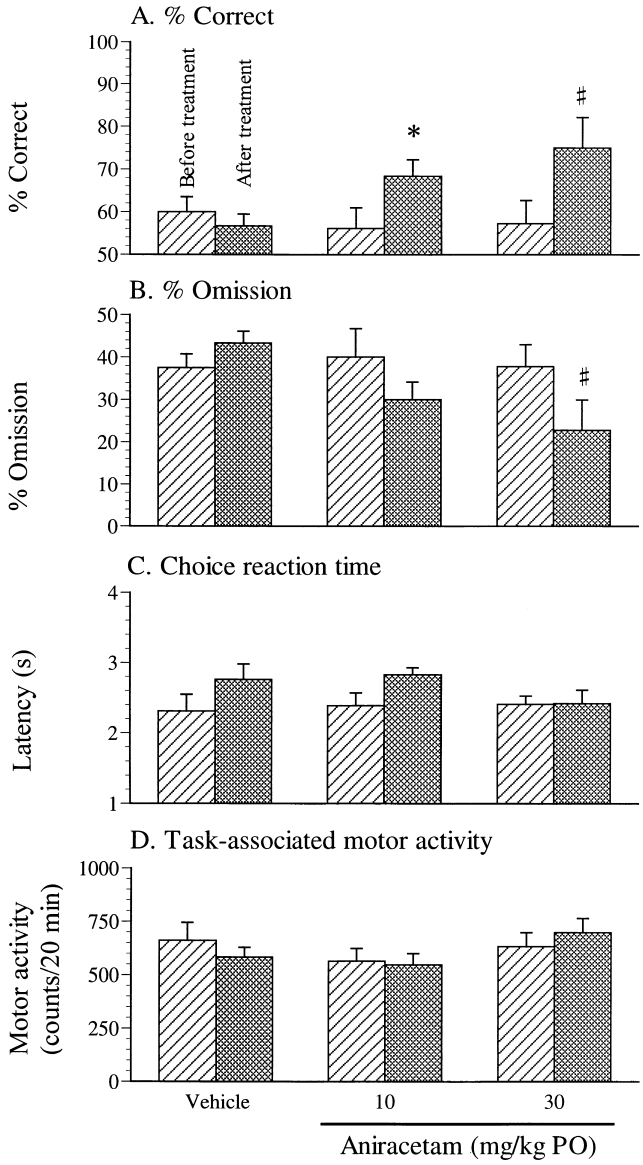

Fig. 2. Effects of repeated administration of aniracetam on the choice reaction performance (A, B and C) and task-associated motor activity (D) in satiated, aged rats. Aniracetam or vehicle was given to animals once daily for 14 consecutive days. Test sessions were conducted on the day prior to the treatment and 1 h after the last and 14th dosage. Data show means ± S.E. ($n=5–7$ rats/group). *,# $P<.05$; compared with pretreatment (Wilcoxon signed-rank test) and vehicle (one-way ANOVA followed by Dunnett's t test), respectively.

The aged rats fed ad libitum outside the task for 64 days were divided into three groups; vehicle and aniracetam (10 and 30 mg/kg, po). Vehicle and aniracetam were administered to the satiated rats once daily for 14 consecutive days. During the treatment periods, animals were not made to

Table 1
Effects of repeated administration of aniracetam on premature response in the choice reaction task performed by satiated, aged rats

Treatment	Dose (mg/kg, po)	DRO		ITI	
		Before	After	Before	After
Vehicle	–	7.5 ± 2.4	2.0 ± 0.71 *	16 ± 3.8	16 ± 5.4
Aniracetam	10	2.2 ± 1.7	2.0 ± 0.65	9.8 ± 1.2	7.3 ± 2.0
	30	3.3 ± 1.4	5.0 ± 1.4	12 ± 2.3	12 ± 3.2

Aniracetam or vehicle was given to animals once daily for 14 consecutive days and a test session began 1 h after the last dosage. Data show means ± S.E. ($n = 5–7$ rats/group).

* $P < .05$, compared with pretreatment (Wilcoxon signed ranks test).

perform the choice reaction task. The repeated treatment of vehicle did not induce a further change in % correct, % omission or CRT (Fig. 2). It did, however, significantly decrease premature responses ($P < .05$) during the DRO period (Table 1). However, this effect was largely due to an unusually high baseline score in one of the animals. Aniracetam dose-dependently reversed the reductions in % correct and increases in % omission [$F(2,16) = 3.95$, $P < .05$ for % correct and $F(2,16) = 3.86$, $P < .05$ for % omission] (Fig. 2). The compound significantly increased % correct scores at 10 mg/kg as compared with pretreatment value. In contrast, aniracetam had no effect on CRT, motor activity or premature responses during either DRO or ITI at any dose (Fig. 2 and Table 1). The repeated administration of aniracetam did not affect animals' weights (Fig. 3).

3. Discussion

In the present study, we found that rats previously trained in the food-reinforced choice reaction task under food restriction stably maintained their performance over a long period, despite their advancing age. Subsequent free feeding satisfied the appetite of these trained rats and resulted in a significant decline in their motivation to respond (lever pressing itself in addition to choice accuracy and responding speed). The release of the trained rats from a long-lasting food restriction led to reductions in performance of the choice reaction task. Coincident significant changes in % correct, % omission and CRT of the task appeared to mainly reflect their reduced food motivation, lack of selective and sustained attention and low vigilance and arousal (Nakamura et al., 1998a). These changes would reduce the motivation to perform and attain the task.

Moreover, we demonstrated that the repeated administration of aniracetam could restore performance reductions caused by satiation. Aniracetam's ability to improve task performance was significant for % correct and % omission but not for CRT. The decrease in % omission was reflected in an increase in % correct lever responses. Thus, these results may be explained by a reversal of drive or motivation, or an increase in sustained attention and vigilance to perform the instrumental operant task even in satiated animals.

We recently observed that treatment with aniracetam (30 and 100 mg/kg, po) for 7 days to fasted aged rats had no effect on daily food intake during a fixed mealtime of 1 h (Tanaka et al., 2000). In the present study, aniracetam did not alter animals' weights, although free feeding for 64 days markedly increased their weights. In addition, if the compound enhances feeding behavior, CRT would probably be shortened in parallel with an increase in % correct. Therefore, it seem unlikely that the effects were due to a single increase in feeding behavior. Rather, it seems likely that aniracetam created a driving force to perform the task, possibly by increasing sustained attention and arousal state. Satiation by free feeding may elicit daily attentional and vigilance failures, and it may reduce motivation. Indeed, it has been shown that aniracetam ameliorated attention deficits and low vigilance induced by various pharmacological manipulations of the central nervous systems in middle-aged rats (Nakamura and Kurasawa, 2000; Nakamura et al., 1998a,b) and possessed a vigilance-enhancing effect in humans (Senin et al., 1993). It seems unlikely, however, that aniracetam affected motor activity/ability or retrieved reference memory on palatable food pellets in satiated rats, since the compound decreased % omission without influencing motor activity. The attentional and vigilance function enhanced by aniracetam may be expressed as small and fine movements in lever responses. In addition, aniracetam did not alter premature response during the both periods of DRO and ITI, suggesting that the compound

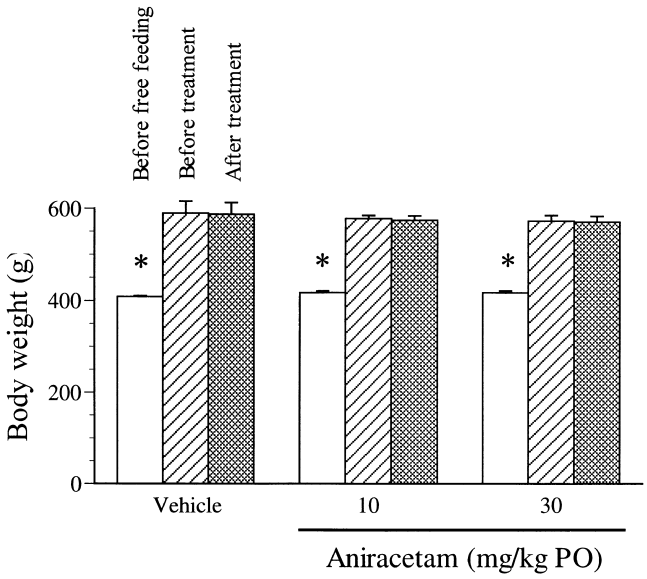

Fig. 3. Effects of repeated administration of aniracetam on body weight in satiated, aged rats. Body weights were measured on the last day of food restriction (the day prior to free feeding) and before and after the treatment for 14 consecutive days. Data show means ± S.E. ($n = 5–7$ rats/group). * $P < .001$; compared with pretreatment (repeated-measures one-way ANOVA followed by Ryan–Einot–Gabriel–Welsch test).

does not induce nonspecific impulsivity. We have recently demonstrated that aniracetam completely blocks impulsive behavior in middle-aged rats evoked by an intracerebroventricular injection of an AMPA receptor antagonist (Nakamura et al., 2000). We have also shown that aniracetam (10–100 mg/kg) has no effect on spontaneous activity in rodents (Himori et al., 1986).

These results suggest that aniracetam may enhance voluntary activity by facilitating the driving force to achieve the operant task unnecessary for satiated rats. In humans, aniracetam alleviated the diminished spontaneity, wakefulness and concentration in Parkinson's disease (Honma et al., 1995) and inhibited the loss of spontaneity, depressed mood and nocturnal delirium associated with cerebral infarction (Otomo et al., 1991). Thus, these findings support a role for aniracetam in accelerating the rehabilitation process to regain ADL spoiled by cerebral infarction (personal communication with Dr. M. Obana).

Increasing evidence suggests positive interactions of aniracetam with multiple central neurotransmitter systems (Martin and Haefely, 1993; Nakamura and Kurasawa, 2000; Nakamura et al., 1998a,b, 2000; Nakamura and Shirane, 1999; Pizzi et al., 1993; Shirane and Nakamura, 2000; Tanaka et al., 1998, 2000), but we have no direct experimental evidence to indicate which specific mechanism is involved in the present study. However, our previous work indicates that aniracetam augments attentional and vigilance processes through a triple activation mechanism of action on central cholinergic, dopaminergic and serotonergic nervous systems (Nakamura and Kurasawa, 2000; Nakamura et al., 1998a,b; Nakamura and Shirane, 1999; Shirane and Nakamura, 2000).

In conclusion, we demonstrated that aniracetam significantly restores satiation-induced motivation reduction as revealed by changes in % correct and % omission. These improvements are most likely due to aniracetam's effects on poor behavioral states (attention deficits and low vigilance) and an augmentation of the motivation necessary for achieving the choice reaction task. These results contribute to our understanding of the clinical efficacy of aniracetam on certain neuropsychiatric effects of cerebral infarction.

References

Himori N, Imai M, Nakamura Y. Potentiating action of the cerebral insufficiency enhancer, aniracetam, on adenosine triphosphate production in rat brain mitochondria. Pharmacol Commun 1992;2:211–6.

Himori N, Watanabe H, Matsuura A, Umeda Y, Kuwahara T, Takemoto C, Takamiya M, Yajima T, Tanaka Y, Nakamura K. General pharmacological properties of aniracetam, a cerebral insufficiency improver. Jpn Pharmacol Ther 1986;14(Suppl. 4):93–128.

Honma H, Takei A, Fukazawa T, Hamada K, Hamada T, Tashiro K. Treatment of Parkinson's disease with aniracetam. Aging Dis 1995;8:96–9.

Katayama T. Spontaneity in dementia: an analysis of 696 institutionalized elderly patients. Keio J Med 1998;47:85–91.

Katsunuma H, Shimizu T, Ogawa K, Kubo H, Ishida H, Yoshihama A. Treatment of insomnia by concomitant therapy with zopiclone and aniracetam in patients with cerebral infarction, cerebroatrophy, Alzheimer's disease and Parkinson's disease. Psychiatry Clin Neurosci 1998;52:198–200.

Kimura M, Okano Y, Inoué S. Effects of aniracetam on impaired sleep patterns in stroke-prone spontaneously hypertensive rats. Psychiatry Clin Neurosci 2000;54:314–6.

Kurasawa M, Tanaka Y, Nakamura K. Anxiolytic, anti-impulsive and antidepressive properties of aniracetam in rodents. Jpn J Pharmacol 2000;82(Suppl. 1):227P.

Kurosu S, Niwa S, Horikoshi R, Takahashi Y, Iizuka K, Takahagi K, Watanabe Y, Yaginuma M, Watanabe K, Kanno M, Hashimoto S. Usefulness of aniracetam for the mental symptoms of chronic cerebral infarction (Second report). Assessment with the GBS and Hamilton Rating Scales. Ger Med 1998;36:1513–20.

Martin JR, Haefely WE. Pharmacology of aniracetam: a novel pyrrolidinone derivative with cognition enhancing activity. Drug Invest 1993;5 (Suppl. 1):4–49.

Nakamura K, Kurasawa M. Serotonergic mechanisms involved in the attentional and vigilance task performance of rats and the palliative action of aniracetam. Naunyn-Schmiedeberg's Arch Pharmacol 2000;361: 521–8.

Nakamura K, Shirane M. Activation of the reticulothalamic cholinergic pathway by the major metabolites of aniracetam. Eur J Pharmacol 1999;380:81–9.

Nakamura K, Kurasawa M, Tanaka Y. Scopolamine model of delirium in rats and reversal of the performance impairment by aniracetam. Drug Dev Res 1998a;43:85–97.

Nakamura K, Kurasawa M, Tanaka Y. Apomorphine-induced hypoattention in rats and reversal of the choice performance impairment by aniracetam. Eur J Pharmacol 1998b;342:127–38.

Nakamura K, Kurasawa M, Shirane M. Impulsivity and AMPA receptors: aniracetam ameliorates impulsive behavior induced by a blockade of AMPA receptors in rats. Brain Res 2000;862:266–9.

Otomo E, Hirai S, Terashi A, Hasegawa K, Tazaki Y, Araki G, Ito E, Nishimura T, Furukawa T. Clinical usefulness of aniracetam for psychiatric symptoms in patients with cerebrovascular disorders: double-blind trial in placebo. J Clin Exp Med 1991;156:143–87.

Pizzi M, Fallacara C, Arrighi V, Memo M, Spano PF. Attenuation of excitatory amino acid toxicity by metabotropic glutamate receptor agonists and aniracetam in primary cultures of cerebellar granule cells. J Neurochem 1993;61:683–9.

Schubert DS, Taylor C, Lee S, Mentari A, Tamaklo W. Physical consequences of depression in the stroke patient. Gen Hosp Psychiatry 1992;14:69–76.

Schut LJ. Dementia following stroke. Clin Geriatr Med 1988;4:767–84.

Senin U, Parnetti L, Cucinotta D, Criscuolo D, Longo A, Marini G. Clinical experience with aniracetam in the treatment of senile dementia of the Alzheimer's type and related disorders. Drug Invest 1993;5(Suppl. 1): 96–105.

Shirane M, Nakamura K. Group II metabotropic glutamate receptors are a common target of *N*-anisoyl-GABA and 1*S*, 3*R*-ACPD in enhancing ACh release in the prefrontal cortex of freely moving SHRSP. Neuropharmacology 2000;39:866–72.

Tanaka Y, Nakamura K, Kurasawa M. Aniracetam attenuates the 5-HT_2 receptor-mediated head-twitch response in rodents as a hallucination model. Drug Dev Res 1998;44:131–9.

Tanaka Y, Kurasawa M, Nakamura K. Recovery of diminished mealtime-associated anticipatory behavior by aniracetam in aged rats. Pharmacol, Biochem Behav 2000;66:827–33.

Vanetzian E. Learning readiness for patients teaching in stroke rehabilitation. J Adv Nurs 1997;26:589–94.