Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmacology 560 (2007) 36–41
www.elsevier.com/locate/ejphar

Effect of NC-1900, an active fragment analog of arginine vasopressin, and inhibitors of arachidonic acid metabolism on performance of a passive avoidance task in mice

Tomoaki Sato [a,*], Takayuki Ishida [a,b], Masahiro Irifune [c], Koh-ichi Tanaka [a], Kenji Hirate [d], Norifumi Nakamura [b], Takashige Nishikawa [a]

[a] Department of Applied Pharmacology, Kagoshima University Graduate School of Medical and Dental Sciences, Sakuragaoka-8, Kagoshima 890-8544, Japan
[b] Department of Oral Maxillofacial Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, Sakuragaoka-8, Kagoshima 890-8544, Japan
[c] Department of Dental Anesthesiology, Graduate School of Biomedical Sciences, Hiroshima University, Kasumi, Hiroshima 734-8533, Japan
[d] Research Laboratories, Nippon Chemiphar Co. Ltd., Saitama 341-0005, Japan

Received 24 October 2006; received in revised form 27 December 2006; accepted 8 January 2007
Available online 19 January 2007

Abstract

In this study, we investigated the effect of administration of inhibitors of each of the arachidonic acid metabolism pathways and the effect of co-administration of these inhibitors with NC-1900, a fragment analog of arginine vasopressin, on step-through passive avoidance task performance. All drugs were administered just after the acquisition trial in the passive avoidance task. Intracerebroventricular (i.c.v.) administration of nordihydroguaiaretic acid (NDGA, 1 and 10 μg), a phospholipase A_2 (PLA_2) and lipoxygenase (LOX) inhibitor, and of arachidonyl trifluoromethyl ketone (ATK, 1 and 10 μg), a specific PLA_2 inhibitor caused reductions in latency on the retention trial. The i.c.v. administration of either of baicalein (0.1–10 μg), a 12-LOX inhibitor, or AA-861 (0.1–10 μg), a 5-LOX inhibitor, did not influence the latency. Intraperitoneal administration of indomethacin (20 mg/kg), a non-specific COX inhibitor, or NS-398 (10 mg/kg), a specific COX-2 inhibitor, impaired performance on the retention trial in the task, while piroxicam (20 mg/kg), a specific COX-1 inhibitor, did not. Subcutaneous administration of NC-1900 (0.1 ng/kg) ameliorated the reduction of latency caused by NDGA, ATK, indomethacin, or NS-398. These results suggested that the COX-2 pathway of arachidonic acid metabolism may be important for learning and/or memory in the passive avoidance task in mice, and that the ameliorating effect of NC-1900, in part, is due to mimicking of the effects of metabolites of the COX-2 pathway.

Keywords: Arginine vasopressin; Learning; Memory; Passive avoidance; Arachidonic acid; NC-1900; Cyclooxygenase

1. Introduction

Arginine vasopressin (AVP_{1-9}) is well-known 9-amino acid peptide hormone that has been shown to facilitate learning and memory (De Wied et al., 1984; De Wied, 1971). AVP is known to have side effects on blood pressure, which has precluded its use as an anti-amnesic drug in clinical therapy. De Wied and coworkers showed that AVP_{4-9}, which is a main metabolite of AVP_{1-9}, has a more potent effect than that of AVP_{1-9} on the consolidation and retrieval components of passive avoidance without affecting the regulation of water balance and blood pressure (Burbach et al., 1983). However, AVP_{4-9} has not previously been used clinically due to its inherent instability in vivo (Sato et al., 2004; Mishima et al., 2003; Brinton et al., 1986).

NC-1900, L-pyroglutamyl-L-asparaginyl-L-seryl-L-prolyl-L-arginylglycinamide (pGlu-Asn-Ser-Pro-Arg-Gly-NH_2), is a newly synthesized AVP_{4-9} analogue in which the cysteine residue of AVP_{4-9} is replaced with a serine residue (Sato et al., 2004; Hori et al., 2002). NC-1900 is a relatively stable peptide with a half life in the blood of rats that is roughly 5.5-fold longer than that of AVP_{4-9} (Hirate et al., 1997). Like AVP_{4-9}, NC-1900 does not affect the regulation of water balance and blood pressure. It has also been reported that the mnemonic effect of NC-1900 is stronger than that of AVP_{4-9} (Sato et al., 2004;

* Corresponding author. Tel.: +81 99 275 6162; fax: +81 99 275 6168.
E-mail address: tomsato@dentb.hal.kagoshima-u.ac.jp (T. Sato).

0014-2999/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2007.01.011

Fujiwara et al., 1997). Since NC-1900 overcomes some of the limitations of AVP_{1-9} and AVP_{4-9}, it may be suitable as an anti-amnesic drug. It is therefore important to explore the mechanism of action of NC-1900 on learning and memory. In recent years, we have suggested that the mnemonic effect of NC-1900 is mediated by the activation of glutamatergic receptors such as NMDA and group I metabotropic receptors through $G_{q/11}$ protein-coupled vasopressin V_{1A} receptor (Sato et al., 2005, 2004).

Researchers have examined signaling pathways in learning and memory and the relationship of these pathways with glutamatergic receptor activity. Long-term potentiation and long-term depression are basic processes of learning and/or memory. It has been proposed that long-term potentiation and long-term depression require sufficient dendritic depolarization to activate the NMDA (*N*-methyl-D-aspartate) subtype of glutamate receptors. NMDA-receptor activation causes increased arachidonic acid release as a result of calcium influx through the NMDA-receptor channel and stimulation of PLA_2 (Teather et al., 2002). Arachidonic acid serves as the precursor for prostanoid and leukotriene production via the actions of cyclooxygenase (COX) and lipoxygenase (LOX), respectively. Prostaglandin H_2 is an intermediate compound formed by the action of COXs and is converted to biologically active prostanoids by specific prostaglandin and thromboxane synthases. In addition, hydroperoxy eicosatetraenoic acid is an intermediate formed by the action of LOXs such as the 5- and 12-LOXs (Normandin et al., 1996). In addition, it has been reported that some prostaglandin and leukotriene receptors activate specific G protein-coupled receptors present on the plasma membrane (Alexander et al., 2001). Therefore it has been suggested that there is a relationship between memory function and metabolites of arachidonic acid pathways. For example, pathways of arachidonic acid metabolism such as the arachidonic acid, COX, and LOX pathways, have been proposed as potential messenger signals in long-term potentiation and memory formation (Normandin et al., 1996; Williams et al., 1989). Previous studies have shown that exogenously applied arachidonic acid facilitates long-term potentiation formation (Williams et al., 1989; Linden et al., 1987) and that application of prostaglandin E_2 (PGE_2) prevents the inhibition of long-term potentiation induced by a specific COX-2 inhibitor (Chen et al., 2002). Hölscher (1995) showed that intracerebral injections of COX inhibitors in chicks 30 min prior to training attenuated retention after a one-trial passive avoidance task. These results suggested that arachidonic acid metabolism is involved in memory formation mediated by glutamatergic receptor activation. From the preceding discussion, it is evident that there are close similarities between the action of NC-1900 and the arachidonic acid metabolism pathway on learning and/or memory formation. Therefore, we speculated that NC-1900 would improve the memory impairment caused by inhibitors of different arachidonic acid metabolism pathways, and that the ameliorating effect of NC-1900 on memory impairment induced by some arachidonic acid metabolism-inhibitors is mediated by enhancement of glutamatergic receptor activity.

The purpose of the present study was to examine which of the arachidonic acid metabolism pathways (PLA_2, LOX, or COX) is more important for memory formation on the step-through passive avoidance task, and whether the administration of NC-1900 improves the amnesia induced by inhibitors of arachidonic acid metabolism.

2. Material and methods

2.1. Animals

Male ddY mice (Kyudou, Ltd., Kumamoto, Japan), 5 to 6 weeks old, were used in the step-through passive avoidance task. The animals were housed with free access to standard food (Clea Japan Inc.) and water in an air-conditioned room at a temperature of 24±1 °C, humidity of 50±10%, and a constant 12 h light/dark cycle (lights on between 7:00 and 19:00). All behavioral experiments were carried out between 9:00 and 17:00. All procedures were approved by the Committee of Animal Experimentation, Kagoshima University.

2.2. Drugs

NC-1900 was provided by Nippon Chemiphar Co. Ltd. (Saitama, Japan); indomethacin, *N*-[2-cyclohexyloxy-4-nitrophenyl]-methanesulfonamide (NS-398), piroxicam, nordihydroguaiaretic acid (NDGA), 2-(12-hydroxydodeca-5, 10-diynyl)-3,5,6-trimethyl-*p*-benzoquinone (AA-861), arachidonyl trifluoromethyl ketone (ATK), and 45% 2-hydroxypropyl-β-cyclodextrin in distilled water (HBC) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). 5,6,7-Trihydroxyflavone (baicalein) was purchased from Cayman Chemical (Ann Arbor, MI, USA).

2.3. Drugs preparation and administration

NC-1900 was dissolved in saline. The other drugs were dissolved in 45% HBC. NC-1900 was subcutaneously (s.c.) injected, and PLA_2 and LOX inhibitors were administered by intracerebroventricular (i.c.v.) injection according to the method of Ueda et al. (1979). COX inhibitors were administered intraperitoneally (i.p.) because the drugs readily penetrate the blood brain barrier via this route (Courade et al., 2001). The control animals for each drug-treated group were injected with saline or vehicle (45% HBC) by the corresponding routes of administration.

2.4. Step-through passive avoidance task

Learning and memory were assessed using a step-through-type passive avoidance test, as previously reported (Sato et al., 2005). In short, a two-compartment step-through-type passive avoidance apparatus was used. The box was divided into bright (10×10×15 cm) and dark compartments (14×18.5×15 cm) by a guillotine door. In each trial, a mouse was placed in the illuminated compartment for a 30 s habituation period, and then a guillotine door was raised to allow entry into the dark chamber. On the pre-exposure session (data not shown), the step-through latency (the length of time spent in the bright compartment after a habituation period) was measured. Mice that stepped through to

the grids of the dark compartment were allowed to remain there for 30 s without electrical stimulation and were then returned to their home cage. The acquisition trial was conducted 24 h after the measurement of pre-exposure latency. When the hind legs of the mice entered into the dark chamber, the guillotine door was closed and electrical foot shock (3 s, 0.08 mA) generated by the shock generator (Muromachi Kikai Co., Tokyo, Japan) was delivered through the grid floor. The retention trial was performed 24 h after the acquisition trial. The time that elapsed prior to entry into the dark compartment (latency) was recorded. The latency was measured for up to 300 s.

2.5. Statistical analysis

Results are expressed as the mean±S.E.M. Data were analyzed using one-way ANOVA with Bonferroni/Dunn test. Statistically significant differences between groups are indicated by $P<0.05$. Data analyses were performed using Stat View 5.0 software (Abacus Concepts, Inc., Berkeley, CA).

3. Results

3.1. Effect of NC-1900 on latency in the passive avoidance task

Fig. 1 shows the effect of 0.1 and 1 ng/kg doses of NC-1900 on latency in the step-through passive avoidance task. The 1 ng/kg dose of NC-1900 prolonged the latency on retention trial in the passive avoidance task (one-way ANOVA [$F(2, 31)=9.2$, $P<0.01$]; post hoc test, $P<0.01$), and consequently, we used the 0.1 ng/kg dose of NC-1900, which alone did not effect the latency in the passive avoidance task, in all subsequent experiments.

3.2. Effect of PLA_2 inhibitors and NC-1900 0.1 ng/kg on the latency impairment induced by PLA_2 inhibitors in the step-through passive avoidance task

One-way ANOVA revealed a significant effect on the retention trial in the passive avoidance task [$F(5, 57)=4.3$, $P<0.01$]. As shown in Fig. 2A, i.c.v. administration of NDGA, an inhibitor of PLA_2 and LOXs (Hölscher and Rose, 1994; Sanfeliu et al., 1990), reduced latency on the retention trial in the passive avoidance task, and subsequent post hoc tests revealed significant differences between the control and 1 μg NDGA group ($P<0.05$), and between the control and 10 μg ($P<0.01$) NDGA groups. The i.p. administration of NC-1900 at a dose of 0.1 ng/kg apparently improved the NDGA-induced impairments of the latency on the retention trial (1 μg NDGA, $P<0.05$; 10 μg, $P<0.05$). Similarly, Fig. 2B shows the effects of ATK, a specific PLA_2 inhibitor (Lee et al., 2003) and of ATK co-administered with NC-1900 on passive avoidance. One-way ANOVA revealed a significant difference among the 6 groups [$F(5, 56)=8.0$, $P<0.01$] on the retention trial. Post hoc tests showed a significant difference between the control and ATK 1 μg ($P<0.05$) and ATK 10 μg ($P<0.01$) groups. The administration of NC-1900 partially prevented the latency decrease caused by 10 μg ATK on the retention trial. In addition, the administration of NC-1900 tended to prevent the latency decrease caused by 1 μg ATK on the retention trial ($P=0.08$), although there was no statistically significant difference between the 2 groups.

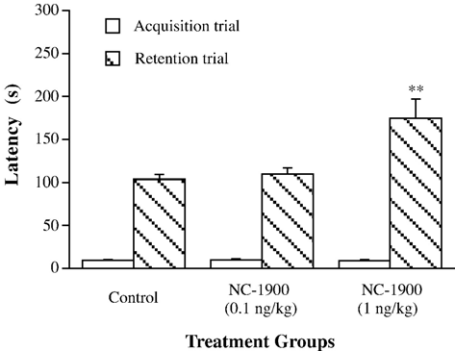

Fig. 1. Effect of 0.1 and 1 ng/kg doses of NC-1900 on latency in the step-through passive avoidance task. NC-1900 was administered (s.c.) subcutaneously just after the acquisition trial. Results are expressed as mean±S.E.M. for 10–12 animals per group. **$P<0.01$ vs. the control group on the retention trial. (Bonferroni/Dunn test).

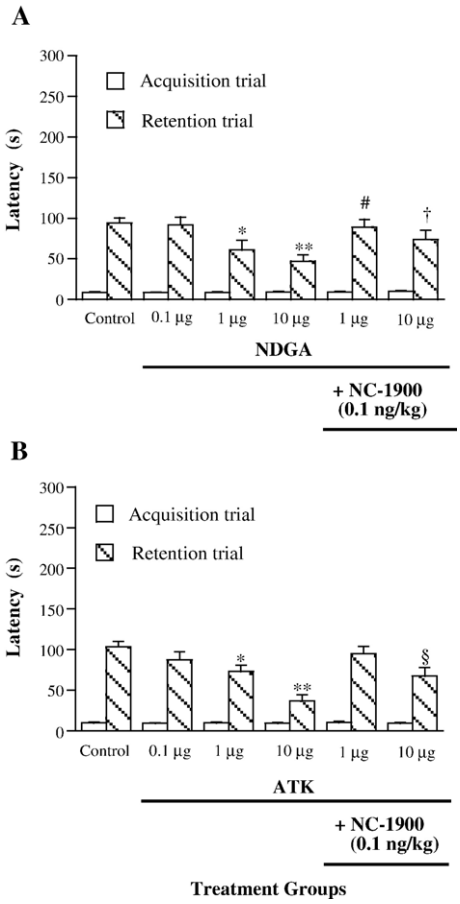

Fig. 2. Effect of PLA_2 inhibitors and NC-1900 on latency in the step-through passive avoidance task. The i.c.v. administration of NDGA (A) and ATK (B) and the s.c. administration of NC-1900 were conducted just after the acquisition trial. Results are expressed as mean±S.E.M. for 10–12 animals per groups. *$P<0.05$, **$P<0.01$ vs. the control group; #$P<0.05$ vs. 1 μg NDGA group; †$P<0.05$ vs. 10 μg NDGA group; and §$P<0.05$ vs. 10 μg BPB group on the retention trial. (Bonferroni/Dunn test), respectively. NDGA = nordihydroguaiaretic acid; ATK = arachidonyl trifluoromethyl ketone.

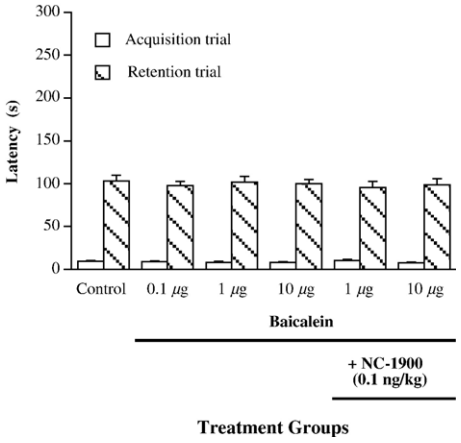

Fig. 3. Effect of baicalein, a 12-LOX inhibitor, alone and in combination with NC-1900 on latency in the step-through passive avoidance task. The i.c.v. administration of baicalein and the s.c. administration of NC-1900 were conducted just after the acquisition trial. Results are expressed as mean ± S.E.M. for 10–12 animals per group.

3.3. Effect of 12-LOX inhibitor alone and in combination with NC-1900 0.1 ng/kg on latency in the step-through passive avoidance task

Administration of baicalein, a 12-LOX inhibitor, did not have a significant effect on the retention trial in the passive avoidance task at any of the doses tested [$F(5, 57)=0.2$, $P=0.9$], nor did co-administration of baicalein (at 1 and 10 μg) with NC-1900 (Fig. 3).

3.4. Effect of 5-LOX inhibitor alone and of co-administration with 0.1 ng/kg of NC-1900 on the latency in the step-through passive avoidance task

As shown in Fig. 4, the administration of AA-861 alone or in combination with NC-1900 had no apparent effect on the retention trial in the passive avoidance task; one-way ANOVA did not show a statistically significant difference among the 6 groups [$F(5, 47)=0.7$, $P=0.7$].

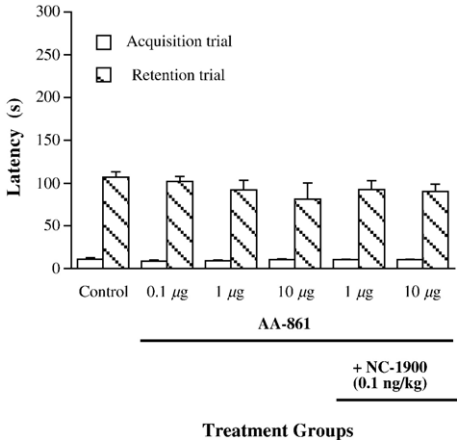

Fig. 4. Effect of AA-861, a 5-LOX inhibitor, alone and in combination with NC-1900 on latency in the step-through passive avoidance task. The i.c.v. administration of AA-861 and the s.c. administration of NC-1900 were conducted just after the acquisition trial. Results are expressed as mean ± S.E.M. for 8–10 animals per group.

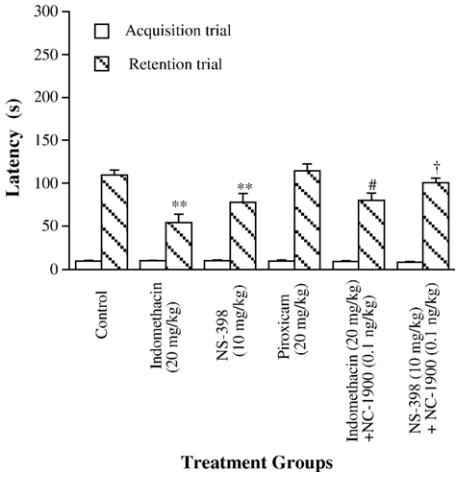

Fig. 5. Effect of COX-inhibitors and NC-1900 on the reduction in step-through passive avoidance task latency induced by indomethacin (a non-specific COX inhibitor) and NS-398 (a specific COX-2 inhibitor). The i.p. administrations of indomethacin, NS-398, and piroxicam, and the s.c. administration of NC-1900 were conducted just after the acquisition trial. Results are expressed as mean ± S.E.M. for 8–13 animals per groups. **$P<0.01$ vs. the control group; #$P<0.05$ vs. 20 mg/kg indomethacin group and †$P<0.05$ vs. 10 mg/kg NS-398 group on the retention trial (Bonferroni/Dunn test), respectively.

3.5. Effect of different COX inhibitors alone and in combination with NC-1900 0.1 ng/kg on latency in the step-through passive avoidance task

Fig. 5 shows the effects of indomethacin (a non-specific COX inhibitor), NS-398 (a specific COX-2 inhibitor), piroxicam (a specific COX-1 inhibitor), and co-administration of indomethacin or NS-398 with NC-1900 in the passive avoidance task. One-way ANOVA revealed a statistically significant difference [$F(5, 57)=7.2$, $P<0.01$] among the 6 groups on the retention trial, and post hoc tests showed significant differences between the control and indomethacin groups ($P<0.01$) and the control and NS-398 ($P<0.01$) groups. The specific COX-1 inhibitor, piroxicam, alone did not show a clear effect on retention trial latency at doses of up to 20 mg/kg. NC-1900 ameliorated the decreased latency induced by indomethacin ($P<0.05$) and NS-398 ($P<0.05$) on the retention trial. Administration of NC-1900 at a dose of 0.1 ng/kg dose did not influence the latency in the piroxicam group (data not shown).

4. Discussion

In the present study, we observed that the administration of PLA_2 inhibitors, but not 5-LOX and 12-LOX inhibitors, decreased the latency on the retention trial in the step-through passive avoidance task. Furthermore, we found that the administration of the non-specific COX inhibitor indomethacin and the specific COX-2 inhibitor NS-398 impaired the latency on the retention trial in the passive avoidance task, while the

specific COX-1 inhibitor piroxicam did not. These results suggest that the COX-2 pathway of arachidonic acid metabolism, but not the LOX or COX-1 pathways, is necessary for learning and/or memory in the step-through passive avoidance task. While our results may seem surprising in light of the widely held belief that non-steroidal anti-inflammatory drugs (NSAIDs) are protective in Alzheimer's disease (McGeer and McGeer, in press), they are in agreement with those of several previous studies (Sharifzadeh et al., 2005; Rall et al., 2003; Teather et al., 2002). These studies, together with our results, suggest that prostaglandins synthesized by the COX-2 pathway may be necessary for learning and/or memory process and may be a more important prostaglandin source than the LOX pathway for step-through passive avoidance task performance. Sharifzadeh et al. (2005) and Rall et al. (2003) also suggested the importance of glutamatergic neurotransmission caused by prostaglandins, especially PGE_2, in learning and memory formation in vivo. Studies of related processes in vitro (Chen et al., 2002; Andreasson et al., 2001; Kaufmann et al., 1996; Yamagata et al., 1993), suggest that PGE_2 modulates glutamatergic neuronal activity and long-term potentiation caused by glutamatergic receptors activation. The present study showed that the administration of PLA_2 inhibitors impaired performance in the passive avoidance task, which is in agreement with results reported by Hölscher and Rose (1994). It appears, therefore, that the blockade of PLA_2 inhibited the production of arachidonic acid, and thereby the production of downstream metabolites. By this mechanism, inhibition of prostaglandin production could result in impairment of long-term potentiation in memory formation and of performance in the step-through task.

Administration of NC-1900 at a dose of 1 ng/kg ameliorated the impairment of performance induced by PLA_2 inhibitors or non-specific- and specific COX inhibitors in the step-through passive avoidance task. Since the administration of NC-1900 improved the impairment induced by COX inhibitors, it is unlikely that the mechanism of action of NC-1900 was due to its mimicking the action of PLA_2, which is an upstream enzyme in the COX pathway. Although we cannot completely rule out other possibilities, one explanation for the ameliorating effect of NC-1900 on the reduction of latency induced by PLA_2 or COX-2 may be due to $G_{q/11}$ protein-coupled receptor activation. In short, NC-1900 may mimic the effect of prostaglandins that are mediated by the activation of $G_{q/11}$ protein-coupled receptors. We previously suggested that NC-1900 improved memory (a function of glutamatergic neurons) through activation of the vasopressin V_{1A} receptor, which is thought to be a $G_{q/11}$ protein-coupled receptor (Sato et al., 2004). In addition, it is well known that PGE_2 receptors have 4 receptor subtypes (prostanoid EP1–4) (Pepicelli et al., 2005) and that 2 (prostanoid EP1 and EP3) of these are thought to $G_{q/11}$ protein-coupled receptors (Alexander et al., 2001). Although the relationship between learning and/or memory formation and the role of different prostaglandin receptors are not well understood, prior studies showed that exogenous PGE_2 can overcome the inhibitory effect of COX-2 inhibitor on long-term potentiation in cultured hippocampal slices (Chen et al., 2002) and suggested that PGE_2-induced memory improvement is mediated by an increase in glutamate receptor activity (Sharifzadeh et al., 2006). PGE_2 receptor activation has also been shown to have neuroprotective or neurotoxic effects mediated by glutamate. For example, prostanoid EP2 and EP3 receptors were shown to mediate neuroprotection in both in vitro and in vivo studies (Bilak et al., 2004; McCullough et al., 2004), and the prostanoid EP1 receptor was shown to possibly contribute to excitotoxicity and focal ischemic brain damage (Ahmad et al., 2006). Although the only known effect of activation of the prostanoid EP1 receptor is that it aggravates NMDA-mediated neuronal toxicity or neuronal damage, activation of the receptor would cause generation of IP_3 and increased levels of intracellular Ca^{2+} (Narumiya et al., 1999). For instance, the activation of prostanoid EP1 receptors would promote neuronal activity. If prostanoid EP1 receptors were excessively activated then they could contribute to the negative effects of PGE_2. However, it is possible that normal stimulation of prostanoid EP1 receptors enhances neuronal activity in the central nervous system. Interestingly, the mechanism of action of prostanoid EP1 receptors resembles the putative mechanism of NC-1900 mediated by vasopressin V_{1A} receptors. We previously suggested that the mnemonic effect of NC-1900, in part, involved activation of the phospholipase C (PLC)-IP_3 pathway (Sato et al., 2005), and in vitro studies suggested that the effect of arginine vasopressin or its metabolite fragments is mediated by the PLC-IP_3 pathway (Omura et al., 1999; Brinton et al., 1994). These reports suggest that the ameliorative effect of NC-1900 on amnesia induced by PLA_2 or COX-2 inhibitors may be caused by enhancement of the PLC-IP_3 signaling pathway, thereby causing the release of Ca^{2+} from IP_3-sensitive Ca^{2+} storage sites. The intracellular elevation of Ca^{2+} levels would then activate glutamatergic neurons, and this process would mimic PGE_2.

Because prostaglandins are thought to be involved in the regulation of acetylcholine receptor sensitivity (Buccafusco et al., 1993), it is also possible that NC-1900 activates cholinergic systems. Indeed, early studies of NC-1900 reported that it ameliorated scopolamine-induced amnesia (Mishima et al., 2003; Fujiwara et al., 1997) and memory deficits caused by β-amyloid protein (Tanaka et al., 1998) in rats. These studies showed that the ability of NC-1900 to improve hypofunction of memory was due to modulation of the cholinergic system. Further studies will be needed to determine whether the cholinergic or glutamatergic system is the main target for NC-1900.

5. Conclusion

Our data demonstrate that the arachidonic acid metabolite pathway, especially the COX-2 pathway, is necessary for memory formation processes, and that the administration of NC-1900 ameliorated memory deficits induced by PLA_2 and non-specific or specific COX-2 inhibitors. It is possible that NC-1900 modulates either the glutamatergic or cholinergic system, and that clinical use of NC-1900 may be effective for diseases involving memory hypofunction.

Acknowledgements

We are grateful to Nippon Chemiphar for the supply of NC-1900. In addition, we express our regret over the death of Dr. Hirate and our thanks for his contributions to the studies on NC-1900. This study was supported, in part, by a Grant-in-Aid for Science Research from the Ministry of Education, Science, and Culture of Japan (Nos. 16591861 and 18592040).

References

Ahmad, A.S., Saleem, S., Ahmad, M., Doré, S., 2006. Prostaglandin EP1 receptor contributes to excitotoxicity and focal ischemic brain damage. Toxicol. Sci. 89, 265–270.

Alexander, S.P.H., Mathie, A., Peters, J.A., 2001. TiPS nomenclature supplement, 12th ed. Elsevier, London, pp. 67–102.

Andreasson, K.I., Kaufmann, W.E., Worley, P.F., Isakson, P., Markowska, A.L., 2001. Age-dependent cognitive deficits and neuronal apoptosis in cyclooxygenase-2 transgenic mice. J. Neurosci. 21, 8198–8209.

Bilak, M., Wu, L., Wang, Q., Haughey, N., Conant, K., St Hillaire, C., Andreasson, K., 2004. PGE_2 receptors rescue motor neurons in a model of amyotrophic lateral sclerosis. Ann. Neurol. 56, 24024–24028.

Brinton, R.E., Gehlert, D.R., Wamsley, J.K., Wan, Y.P., Yamamura, H.I., 1986. Vasopressin metabolite, AVP4–9, binding sites in the brain distribution distinct from that of parent peptides. Life Sci. 38, 443–452.

Brinton, R.D., Gonzalez, T.M., Cheung, W.S., 1994. Vasopressin-induced calcium signaling in cultured hippocampal neurons. Brain Res. 661, 274–282.

Buccafusco, J.J., Lapp, C.A., Aronstam, R.S., Hays, A.C., Shuster, L.C., 1993. Role of prostanoids in the regulation of central cholinergic receptor sensitivity. J. Pharmacol. Exp. Ther. 266, 314–322.

Burbach, J.P.H., Kovacs, G.L., De Wied, D., Van Nispen, J.W., Greven, H.M., 1983. A major metabolites of arginine–vasopressin in the brain is highly potent neuropeptides. Science 221, 1310–1312.

Chen, C., Magee, J.C., Bazan, N.G., 2002. Cyclooxygenase-2 regulates prostaglandin E_2 signaling in hippocampal long-term synaptic plasticity. J. Neurophysiol. 87, 2851–2857.

Courade, J.P., Besse, D., Delchambre, C., Hanoun, N., Hamon, M., Eschalier, A., Caussade, F., Cloarec, A., 2001. Acetaminophen distribution in the rat central nervous system. Life Sci. 69, 1455–1464.

De Wied, D., 1971. Long term effect of vasopressin on the maintenance of conditioned avoidance response in rats. Nature 232, 58–60.

De Wied, D., Gaffori, O., Van Ree, J.M., De Jong, W., 1984. Central target for the behavioural effects of vasopressin neuropeptides. Nature 308, 276–278.

Fujiwara, M., Ohgami, Y., Inada, K., Iwasaki, K., 1997. Effect of active fragments of arginine–vasopressin on the disturbance of spatial cognition in rats. Behav. Brain Res. 83, 91–96.

Hirate, K., Hirano, M., Nakajima, Y., Hiyama, A., Maeda, O., Asakura, W., 1997. No. 302, a newly synthesized [$pGlu^4$,Cyt^6]AVP(4–9) analogue, prevents the disruption of avoidance behavior. Behav. Brain Res. 83, 205–208.

Hölscher, C., 1995. Inhibitors of cyclooxygenases produce amnesia for a passive avoidance task in the chick. Eur. J. Neurosci. 7, 1360–1365.

Hölscher, C., Rose, S.P.R., 1994. Inhibitors of phospholipase A_2 produce amnesia for passive avoidance task in chick. Behav. Neural Biol. 61, 225–232.

Hori, E., Uwano, T., Tamura, R., Miyake, N., Hishijo, H., Ono, T., 2002. Effects of a novel arginine–vasopressin derivative, NC-1900, on the spatial memory impairment of rats with transient forebrain ischemia. Cogn. Brain Res. 13, 1–15.

Kaufmann, W.E., Worley, P.F., Pegg, J., Bremer, M., Isakson, P., 1996. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc. Natl. Acad. Sci. U. S. A. 93, 2317–2321.

Lee, D., Won, J.H., Auh, C.-K., Park, Y.M., 2003. Purification and characterization of a cytosolic phospholipase A_2 from rat liver. Mol. Cells 16, 361–367.

Linden, D.J., Sheu, F.S., Murakami, K., Routenberg, A., 1987. Enhancement of long-term potentiation by *cis*-unsaturated fatty acid: relation to protein kinase C and phospholipase A_2. J. Neurosci. 7, 3783–3792.

McCullough, L., Wu, L., Haughey, N., Liang, X., Hand, T., Wang, Q., Breyer, R.M., Andreasson, K., 2004. Neuroprotective function of the PGE_2 EP2 receptor in cerebral ischemia. J. Neurosci. 24, 257–268.

McGeer, P.L., McGeer, E.G. in press. NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies. Neurobiol. Aging, doi:10.1016/j.neurobiolaging.2006.03.013.

Mishima, K., Tsukikawa, H., Miura, I., Inada, K., Abe, K., Matsumoto, Y., Egashira, N., Iwasaki, K., Fujiwara, M., 2003. Ameliorative effect of NC-1900, a new $AVP_{4–9}$ analog, through vasopressin V_{1A} receptor on scopolamine-induced impairments of spatial memory in the eight-arm radial maze. Neuropharmacology 44, 541–552.

Narumiya, S., Sugimoto, Y., Ushikubi, F., 1999. Prostanoid receptors: structures, properties, and functions. Physiol. Rev. 79, 1193–1226.

Normandin, M., Gagne, J., Bernard, J., Elie, R., Miceli, D., Baudry, M., Massicotte, G., 1996. Involvement of the 12-lipoxygenase pathway of arachidonic acid metabolism in homosynaptic long-term depression of the rat hippocampus. Brain Res. 730, 40–46.

Omura, T., Nabekura, J., Akaike, N., 1999. Intracellular pathways of V_1 and V_2 receptors activated by arginine vasopressin in rat hippocampal neurons. J. Biol. Chem. 274, 32762–32770.

Pepicelli, O., Fedele, E., Berardi, M., Raiteri, M., Levi, G., Greco, A., Ajmone-Cat, M.A., Minghetti, L., 2005. Cyclo-oxygenase-1 and -2 differently contribute to prostaglandin E2 synthesis and lipid peroxidation after in vivo activation of *N*-methyl-D-aspartate receptors in rat hippocampus. J. Neurochem. 93, 1561–1567.

Rall, J., Mach, S.A., Dash, P.K., 2003. Intrahippocampal infusion of a cyclooxygenase-2 inhibitor attenuates memory acquisition in rats. Brain Res. 968, 273–276.

Sanfeliu, C., Hunt, A., Patel, A., 1990. Exposure to *N*-methyl-D-aspartate increases release of arachidonic acid in primary cultures of rat hippocampal neurons and not in astrocytes. Brain Res. 526, 241–248.

Sato, T., Tanaka, K., Teramoto, T., Ohnishi, Y., Hirate, K., Irifune, M., Nishikawa, T., 2004. Facilitative effect of a novel AVP fragment analog, NC-1900, on memory retention and recall in mice. Peptides 25, 1139–1146.

Sato, T., Ishida, T., Tanaka, K., Chowdhury, N., Irifune, M., Hirate, K., Mimura, T., Nishikawa, T., 2005. Glutamate antagonists attenuate the action of NC-1900, a vasopressin fragment analog, on passive avoidance task performance in mice. Peptides 26, 893–897.

Sharifzadeh, M., Naghdi, N., Khosrovani, S., Ostad, S.N., Sharifzadeh, K., Roghani, A., 2005. Post-training intrahippocampal infusion of the COX-2 inhibitor celecoxib impaired spatial memory retention in rats. Eur. J. Pharmacol. 511, 159–166.

Sharifzadeh, M., Tavasoli, M., Soodi, M., Mohammadi-Eraghi, S., Ghahremani, M.H., Roghani, A., 2006. A time course analysis of cyclooxygenase-2 suggests a role in spatial memory retrieval in rats. Neurosci. Res. 54, 171–179.

Tanaka, T., Yamada, K., Senzaki, K., Narimatsu, H., Nishimura, K., Kameyama, T., Nabeshima, T., 1998. NC-1900, an active fragment analog of arginine vasopressin, improves learning and memory deficits induced by β-amyloid protein in rats. Eur. J. Pharmacol. 352, 135–142.

Teather, L.A., Packard, M.G., Bazan, N.G., 2002. Post-training cyclooxygenase-2 (COX-2) inhibition impairs memory consolidation. Learn. Mem. 9, 41–47.

Ueda, H., Amano, H., Shiomi, H., Takagi, H., 1979. Comparison of the analgesic effects of various opioid peptides by a newly devised intracisternal injection technique in conscious mice. Eur. J. Pharmacol. 56, 265–268.

Williams, J.H., Errington, M.L., Lynch, M.A., Bliss, T.V., 1989. Arachidonic acid induces a long-term activity-dependent enhancement of synaptic transmission in the hippocampus. Nature 341, 739–742.

Yamagata, K., Andreasson, K.I., Kaufmann, W.E., Barnes, C.A., Worley, P.F., 1993. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. Neuron 11, 371–386.