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ORIGINAL ARTICLE

N-Methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors involved in the induction of sedative effects under an acute stress in neonatal chicks

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Abstract Glutamate, an excitatory amino acid, acts at several glutamate receptor subtypes. Recently, we reported that central administration of glutathione induced hypnosis under stressful conditions in neonatal chicks. Glutathione appears to bind to the *N*-methyl-D-aspartate (NMDA) receptor. To clarify the involvement of each glutamate receptor subtype during stressful conditions, intracerebroventricular (i.c.v.) injection of several glutamate receptor agonists was given to chicks under social separation stress. Glutamate dose-dependently induced a hypnotic effect. NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate are characterized as ionotropic glutamate receptors (iGluRs). Although NMDA also induced sleep-like behavior or sedative effects, the potency of NMDA was less than that of glutamate. AMPA tended to decrease distress vocalizations induced by acute stress and brought about a sedative effect. Kainate and (S)-3, 5-dehydroxyphenylglycine, which is a metabotropic glutamate receptor agonist, had no influence on chick behavior. Thus, it is suggested that the iGluRs, NMDA and AMPA, are important in inducing hypnosis and sedation under acute stress in chicks.

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Introduction

Excitatory amino acids (EAAs), including glutamate and aspartate, act as neurotransmitters in the central nervous system (CNS). They can induce neuronal activity with powerful stimulatory effects (Monaghan et al. 1989). Glutamate receptors are divided into two groups: ionotropic and metabotropic glutamate receptors. Ionotoropic glutamate receptors (iGluRs), which form ion channels, include three main classes: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate and *N*-methyl-D-aspartate (NMDA) receptors. The NMDA receptor is usually blocked by Mg^{2+}. When the synaptic membrane is slightly depolarized, e.g., by previous activation of AMPA and kainate receptors, the Mg^{2+} block of the NMDA receptor is removed. The NMDA receptor is activated after binding of an agonist (Bleich et al. 2003). On the other hand, the metabotropic glutamate receptors (mGluRs) are coupled to GTP-binding proteins, and regulate the production of intracellular messengers. The mGluRs have eight members (mGluR1-8), categorized into three groups based on sequence homology, second messenger coupling and pharmacology. Group I includes mGluR1 and 5, group II is mGluR2 and 3 and group III is mGluR4, 6, 7 and 8. Group I mGluRs are localized postsynaptically and predominantly activate phospholipase C. Group II and III mGluRs are localized in presynaptic densities and inhibit adenylyl cyclase activity. They contribute to the regulation of synaptic plasticity and transmission (De Blasi et al. 2001; Kew and Kemp 2005).

In the previous paper, it was shown that reduced glutathione (γ-L-glutamate-L-cysteinylglycine; GSH), which is a tripeptide consisting of glutamate, cysteine and glycine, induced hypnosis during a stressful condition in neonatal chicks, and this effect involved the NMDA receptor (Yamane et al. 2007). Furthermore, glutathione appears to play a role as a neurotransmitter or neuromodulator, as it can bind to the NMDA receptor and other glutamate receptors via its γ-glutamyl moiety and thereby induce the movement of intracellular Ca^{2+} (Janáky et al. 1999). Thus, it is hypothesized that glutamate receptors are involved in sleep regulation in neonatal chicks.

The distribution of iGluRs ligand binding sites is markedly different in the chick brain as shown using autoradiography (Henley et al. 1989). Although [^{3}H]L-glutamate, [^{3}H]AMPA and [^{3}H]kainate label strongly the molecular layer of the cerebellum, the density of [^{3}H]kainate is particularly intense. [^{3}H]L-Glutamate densely labels the telencephalon, particularly the neostriatum. [^{3}H]AMPA binding sites are densely located in the hippocampus, and are also extensively distributed in the telencephalon. These regions correspond with brain structures involved in the regulation of stress, including anxiety and fear (Camargo 2001; LeDoux 1998; McNaughton 1997). In general, the NMDA receptor usually coexists with the AMPA receptor in the postsynaptic membrane (Nadler 2007). In addition, the structure and function of mGluRs has been demonstrated in several experiments in chicks (Hyson 1998; Salinska 2006; Zirpel et al. 1995).

In past studies, behavioral experiments were run using neonatal chicks under social stress (Feltenstein et al. 2003; Panksepp et al. 1980; Sahley et al. 1981). When chicks are isolated, they express characteristic stress-related behaviors which include increased distress vocalizations and spontaneous activity. Namely, time for active wakefulness is increased and the reverse is true for sleeping behavior. Therefore, the effect of drugs which have antianxiety effects can be screened observing the behavior of chicks under isolation stress.

The aim of present study was to clarify the contribution of glutamate receptors for sedative and hypnotic effects under acute stress in chicks. In the present experiment we focused on NMDA and AMPA as iGluRs agonists. Furthermore, since group I mGluRs have an excitatory neurotransmission similar to iGluRs, the group I selective mGluRs agonist (S)-3, 5-dehydroxyphenylglycine (DHPG) was also applied.

Materials and methods

One-day-old male layer-type chicks (Julia) were purchased from a local hatchery (Murata Hatchery, Fukuoka, Japan) and housed in a windowless room at a constant temperature of 30 ± 1°C. Continuous lighting was provided. The chicks were given free access to a commercial starter diet (AX, Toyohashi Feed and Mills Co Ltd., Aichi, Japan) and water. Chicks were reared in a group (20–25/cage) until the day before the experiment. On the day of the experiment, chicks (5-day-old) were assigned to treatment groups based on their body weight in order to produce uniform treatment groups. Experimental procedures followed the guidance for Animal Experiments in the Faculty of Agriculture and in the Graduate Course of Kyushu University and the Law (No. 105) and Notification (No. 6) of the Government.

L-Glutamate and NMDA were purchased from Sigma (St. Louis, MO, USA), and (RS)-AMAP, kainate and the selective group I selective mGluRs agonist DHPG were purchased from TOCRIS (Cookson, Ellisville, MO, USA). Drugs were dissolved in 0.85% saline containing 0.1% Evans Blue solution and stirred well using a vortex.

Intracerebroventricular (i.c.v.) injections were made using a microsyringe according to the method of Davis et al. (1979). This system does not cause significant discomfort for chicks (Koutoku et al. 2005). All experiments were done during the daytime (9:00–17:00). Chicks were randomly given several doses of drugs: glutamate (0.2, 0.4 and 0.8 μmol) in Experiment 1, NMDA (0.5, 1.0 and 2.0 nmol) in Experiment 2, AMPA (50, 100 and 150 pmol) in Experiment 3, kainite (0.25, 0.5 and 1 nmol) in Experiment 4 and DHPG (0.01, 0.1 and 1 nmol) in Experiment 5. Saline containing 0.1% Evans Blue was used as the control in all experiments. Each dosage was determined by pilot studies. The number of chicks used for the analysis in each group is as following: Experiment 1 was 0.2 μmol—7, 0.4 μmol—7 and 0.8 μmol—7, Experiment 2 was 0.5 nmol—7, 1.0 nmol—7 and 2.0 nmol—8, Experiment 3 was 50 pmol—6, 100 pmol—7 and 150 pmol—7, Experiment 4 was 0.25 nmol—7, 0.5 nmol—7, 1 nmol—7, Experiment 5 was 0.01 nmol—7, 0.1 nmol—7 and 1 nmol—7. The controls were 7 in Experiments 1–3 and 5 and were 8 in Experiment 4. An acrylic device was used to hold the head of chicks. The head holder with a hole in the head plate of the device was accommodated for the 26-gauge needle of a Hamilton microsyringe into the lateral ventricle, and a drug was intracerebroventricularly injected by the syringe. The injection depth was approximately 0.6 cm from the bottom of the head plate. After the injection, chicks were immediately placed in an acrylic monitoring cage (40 cm × 30 cm × 20 cm), and behavioral observations were made for 10 min. During this period, chicks were deprived of feed and water. Chick vocalizations were recorded using a computer with the software Windows Media Player (Microsoft Corporation, WA, USA) and the number of distress vocalizations was counted using Gretchen software (Excla Inc., Saitama,

Japan). Video cameras were positioned to record the behaviors of chicks from three different directions. The monitoring systems were set in a separate room to avoid disturbing the animals. Data were saved on a DVD disk for later review. Based on the method by van Luijtelaar et al. (1987), the chick's behaviors were classified into four categories: (1) active wakefulness; (2) standing/sitting motionless with eyes open; (3) standing motionless with eyes closed; (4) sitting motionless with head drooped (sleeping posture). They demonstrated a correlation between sleeping posture and electrophysiological sleep with EEG measurements (van Luijtelaar et al. 1987; Fig. 1).

Finally, the chicks were decapitated after an overdose of sodium pentobarbital. The brains were removed and the location of the Evans Blue dye was confirmed. Data of chicks without dye in the lateral ventricle were deleted.

In the analysis of distress vocalizations and behavioral categories, one-way ANOVA was used, and Tukey-Kramer's test was done as a post hoc test. Significance implies $P < 0.05$. Values are presented as means with SEM Regression equations were fitted to the behavioral observation data. Statistical analysis was made using a commercially available package, StatView (Version 5, SAS Institute, Cary, NC, USA, 1998).

Results

Experiment 1: i.c.v. injection of glutamate

Figure 2a shows the effect of several doses of glutamate on total distress vocalizations during the 10 min isolation period. A significant effect of glutamate were found on distress vocalizations [F (3, 24) = 21.950, $P < 0.0001$]. Distress vocalizations were dose-dependently decreased by i.c.v. glutamate. Table 1 shows the effect of glutamate on the behavioral observations during the 10 min isolation. The time of active wakefulness decreased dose-dependently [F (3, 24) = 24.645, $P < 0.0001$] [active wakefulness (second/10 min) = 526 (SE = 41) − 692 (SE = 89) × ($R^2 = 0.701$, $P < 0.0001$)]. On the other hand, the time of sitting motionless with head drooped increased gradually [F (3, 24) = 17.514, $P < 0.0001$] [sleeping posture (second/10 min) = −11 (SE = 34) + 553 (SE = 74) × ($R^2 = 0.684$, $P < 0.0001$)].

Experiment 2: i.c.v. injection of NMDA

Figure 2b shows the effect of several doses of NMDA on total distress vocalizations. NMDA dose-dependently affected distress vocalizations [F (3, 25) = 21.171, $P < 0.0001$]. Table 1 shows the effect of NMDA on the behavioral observation during the 10 min isolation. The time of active wakefulness decreased dose-dependently [F (3, 25) = 19.791, $P < 0.0001$] [active wakefulness (second/10 min) = 552 (SE = 38) − 223 (SE = 32) × ($R^2 = 0.640$, $P < 0.0001$)]. In contrast, the time of standing/sitting motionless with eyes open increased dose-dependently [F (3, 25) = 8.428, $P < 0.001$] [standing/sitting motionless with eyes open (second/10 min) = 58 (SE = 35) + 140 (SE = 30) × ($R^2 = 0.450$, $P < 0.0001$)].

Experiment 3: i.c.v. injection of AMPA

Figure 2c shows the effect of several doses of AMAP on total distress vocalizations during the 10 min isolation. AMPA tended to dose-dependently decrease distress vocalizations but this effect was not significant [F (3, 23) = 3.022, $P = 0.0503$]. Table 1 shows the effect

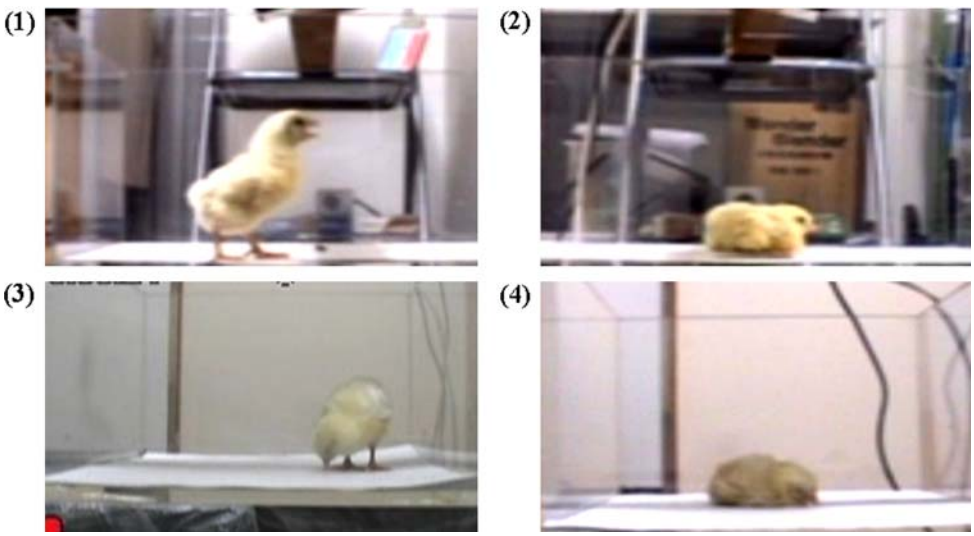

Fig. 1 Four categories of postures. (1) Active wakefulness; vocalizing and active or passive behavior and sitting with head movements. (2) Standing/sitting motionless with eyes open without vocalizing and head movements. (3) Standing motionless with eyes closed. (4) Sitting motionless with head drooped (sleeping posture); this behavior is observed when hypnotic effect is induced

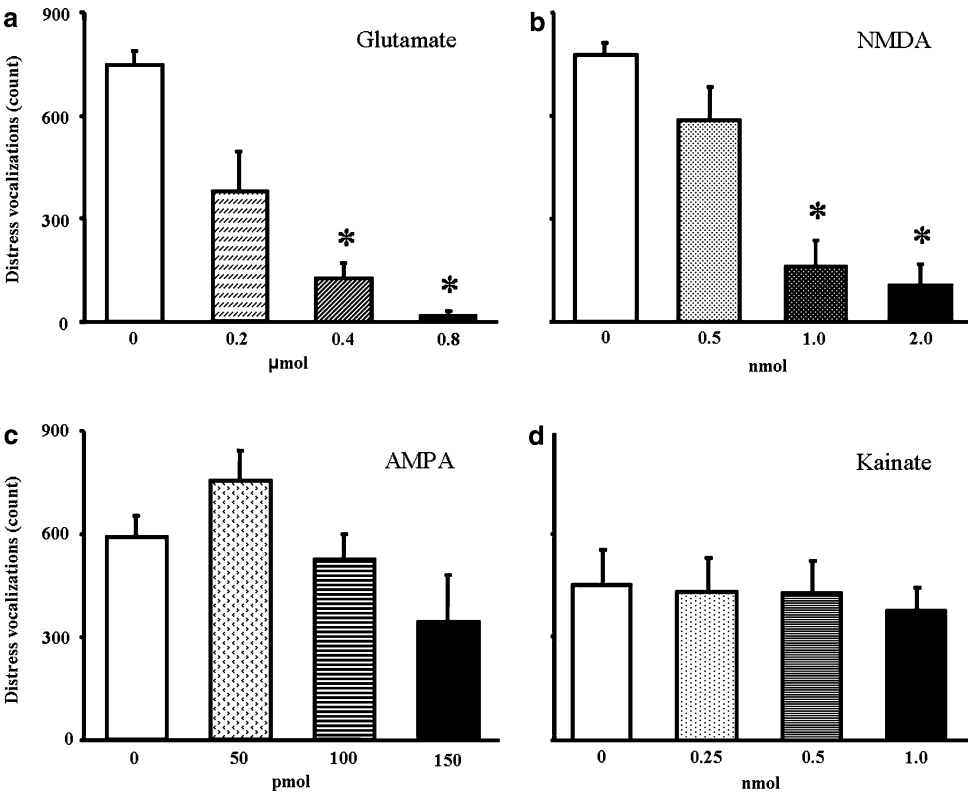

Fig. 2 Effect of i.c.v. injection of iGluR agonists on total distress vocalizations during a 10 min isolation period in chicks. Results are expressed as means with SEM Glutamate (count/10 min) = 621 (SE = 62) − 868 (SE = 135) × ($R^2 = 0.613$, $P < 0.0001$). NMDA (count/10 min) = 708 (SE = 64) − 342 (SE = 54) × ($R^2 = 0.596$, $P < 0.0001$). AMPA (count/10 min) = 691 (SE = 83) − 2 (SE = 1) × ($R^2 = 0.158$, $P < 0.05$). *Significant difference when compared with the control at $P < 0.05$

of several doses of AMPA on the behavioral observation during the 10 min isolation. The time of active wakefulness decreased dose-dependently [F (3, 23) = 4.862, $P < 0.01$] [active wakefulness (second/10 min) = 600 (SE = 51) − 2 (SE = 1) × ($R^2 = 0.309$, $P < 0.01$)]. On the other hand, the behavior of standing motionless with eyes closed and sleeping posture were found only in the 150 pmol AMPA group, and the time of sleeping posture exhibited a significant increase [F (3, 23) = 6.512, $P < 0.01$] [sleeping posture (second/10 min) = −40 (SE = 38) + 1 (SE = 0.4) × ($R^2 = 0.274$, $P < 0.01$)].

Experiment 4: i.c.v. injection of kainate

Figure 2d and Table 1 show the effect of several doses of kainate on total distress vocalizations and on the behavioral observations during the 10 min isolation, respectively. No significant effects were found in total distress vocalizations ($P = 0.9473$). All groups receiving kaiante were comparable to the control group in behavioral observation.

Experiment 5: i.c.v. injection of DHPG

No significant ($P = 0.7518$) effects were found in total distress vocalizations (control 885 ± 43; 0.01 nmol, 825 ± 53; 0.1 nmol, 857 ± 46; and 1 nmol, 835 ± 16). Table 1 shows the effect of several doses of DHPG on the behavioral observations the during the 10 min isolation, respectively. All groups receiving DHPG spent the most time in active wakefulness, and they were comparable to the control group. Standing motionless with eyes closed and sleeping posture were not found in these groups.

Discussion

The i.c.v. injection of glutamate, NMDA and AMPA attenuated total distress vocalizations and induced sedation in the present study. In contrast, previous studies showed that localized infusion of glutamate-induced vocalizations in cats (Bandler 1982) and squirrel monkeys (Jürgens and Richter 1986). Additionally, the injection of NMDA, AMPA and kainate into the substantia innominata/lateral preoptic area of rats dose-dependently stimulated locomotion (Shreve and Uretsky 1988). Lateral hypothalamic injection of kainate also increased locomotor activity in rats (Stanley et al. 1993; Hettes et al. 2007). Further, when injected intracranially to restricted brainstem regions, NMDA elicited locomotion in decerebrate geese and ducks (Sholomenko et al. 1991). On the other hand, injection of glutamate into the lateral hypothalamus increases sleeping time (Stanley et al. 1993). The difference between these studies and the present results may be due to species differences or the site of injection.

The i.c.v. injection of glutamate in Experiment 1 dose-dependently decreased distress vocalizations in isolated

Table 1 Effect of i.c.v. injection of several doses of glutamate, NMDA, AMPA, kainate and DHPG on various behavioral categories of chicks during 10 min post-injection

Drugs	Active wakefulness	Standing/sitting motionless with eyes open	Standing motionless with eyes closed	Sitting motionless with head drooped (sleeping posture)
L-Glutamate				
0 μmol	575 ± 15	25 ± 15	0 ± 0	0 ± 0
0.2 μmol	382 ± 85*	120 ± 39	11 ± 11	87 ± 53
0.4 μmol	159 ± 46*	205 ± 44*	29 ± 29	207 ± 69*
0.8 μmol	19 ± 15*	134 ± 23	10 ± 10	437 ± 26*
NMDA				
0 nmol	560 ± 13	40 ± 13	0 ± 0	0 ± 0
0.5 nmol	490 ± 54	110 ± 54	0 ± 0	0 ± 0
1 nmol	238 ± 57*	262 ± 41*	0 ± 0	100 ± 52
2 nmol	134 ± 46*	314 ± 53*	0 ± 0	152 ± 71
AMPA				
0 pmol	551 ± 16	49 ± 16	0 ± 0	0 ± 0
50 pmol	568 ± 23	32 ± 23	0 ± 0	0 ± 0
100 pmol	471 ± 49	129 ± 49	0 ± 0	0 ± 0
150 pmol	281 ± 101*	102 ± 34	10 ± 7	207 ± 79*
Kainate				
0 nmol	468 ± 54	75 ± 22	21 ± 21	43 ± 43
0.25 nmol	404 ± 61	86 ± 32	19 ± 12	91 ± 43
0.5 nmol	454 ± 62	68 ± 24	19 ± 19	60 ± 40
1 nmol	558 ± 20	31 ± 13	0 ± 0	11 ± 11
DHPG				
0 nmol	591 ± 4	9 ± 4	0 ± 0	0 ± 0
0.01 nmol	585 ± 4	15 ± 4	0 ± 0	0 ± 0
0.1 nmol	589 ± 9	11 ± 9	0 ± 0	0 ± 0
1 nmol	593 ± 4	7 ± 4	0 ± 0	0 ± 0

Values are mean ± SEM in seconds

* Significantly different when compared with control at $P < 0.05$

L-Glutamate; Active wakefulness (second/10 min) = 526 (SE = 41) – 692 (SE = 89) × ($R^2 = 0.701$, $P < 0.0001$) and sleeping posture (second/10 min) = −11 (SE = 34) + 553 (SE = 74) × ($R^2 = 0.684$, $P < 0.0001$)

NMDA; Active wakefulness (second/10 min) = 552 (SE = 38) − 223 (SE = 32) × ($R^2 = 0.640$, $P < 0.0001$) and standing/sitting motionless with eyes open (second/10 min) = 58 (SE = 35) + 140 (SE = 30) × ($R^2 = 0.450$, $P < 0.0001$)

AMPA; Active wakefulness (second/10 min) = 600 (SE = 51) − 2 (SE = 1) × ($R^2 = 0.309$, $P < 0.01$) and sleeping posture (second/10 min) = −40 (SE = 38) + 1 (SE = 0.4) × ($R^2 = 0.274$, $P < 0.01$)

chicks similarly to that observed by Panksepp et al. (1988) who injected glutamate at doses from 25 to 500 μg. In contrast to the results of Experiment 2, Panksepp et al. (1988) reported the administration of NMDA (0.1, 0.25, 0.5 and 1.0 μg) had no effect on the number of vocalizations. Differences in the time for behavioral observation, experiment conditions, or genetic line of chicks may contribute to the contrasting results for vocalizations. For example, the stress response differs between meat- and layer-type neonatal chicks, being relatively higher in the layer-type used in the present study (Saito et al. 2005).

Although i.c.v. injection of EAA glutamate, and the glutamate analogue NMDA, induced sedation in chicks in the present study, the behavioral results for the two compounds were somewhat different. NMDA induced an increase in the time spent standing/sitting motionless with eyes open while glutamate increased the time of sleeping posture. AMPA had a tendency to decrease wakefulness activity and increase sleep-like behavior. The central administration of kainate (0.05, 0.1, 0.25 and 0.5 μg) had no effect under stressful condition in chicks (Panksepp et al. 1988). In Experiment 4, no significant effect of kainate was also observed compared with the control in this study. Henley et al. (1989) demonstrated the distribution of iGluRs ligand binding sites in the chick brain using autoradiography. The binding sites of NMDA and AMPA are related to the brain regions of stress

response. However, kainite binding sites is mainly the molecular layer of the cerebellum which is not mainly stress-related region in the brain. In general, the NMDA receptor usually coexists with the AMPA receptor in the postsynaptic membrane (Nadler 2007). Therefore, kainate may not be related to stress response. In any case, kainate, in the doses used here, appears to have no sedative effect against isolation stress in chicks. It is suggested that the hypnotic effects of glutamate involved not only the NMDA receptor, but also the AMPA receptor. In the present study, the group I selective mGluRs agonist DHPG was applied, but no effect on sleeping posture was detected. Although we did not investigate the effect of group II and III mGluRs, the data supports the theory that the iGluRs NMDA and AMPA, but not kainate, are related to sleep-induction in neonatal chicks.

γ-Aminobutytic acid (GABA) and taurine are representative inhibitory amino acids. Both the GABAergic system and taurine exert anti-anxiety actions (Zarrindast et al. 2001; Zhang and Kim 2007). Several experiments have shown that NMDA and glutamate can cause the release of GABA from cultured neurons in mice and rats (Drejer et al. 1987; Harris and Miller 1989; Reynolds et al. 1989). In addition, an increase of taurine is induced when NMDA is delivered into the medio-rostral neostriatum/hyperstriatum ventral using microdialysis in chicks (Gruss et al. 1999). Therefore, the sedative effects seen in this experiment may be due to the glutamate triggered release of GABA. Indeed, it has been confirmed that the i.c.v. injection of GABA induced sedative effect under acute stress in chicks (Shigemi et al. unpublished data).

The i.c.v. injection of reduced glutathione (GSH) induced hypnosis under an acute stress in neonatal chicks (Yamane et al. 2007). Sleeping-like posture was increased dose-dependently in chicks by the injection of GSH (0.5, 1.0 and 2.0 μmol). Yamane et al. (2007) speculated that a hypnotic effect of GSH may be mediated through the NMDA receptor, since GSH binds to NMDA receptors (Janáky et al. 1999). AMPA had a tendency to induce sedation in the present study. However, GSH is not an effective competitive ligand for AMPA receptor (Janáky et al. 1999). Therefore, it appears unlikely that the induction of hypnosis by GSH involves activation of the AMPA receptor.

Similarly, glutamate, which exhibited the same effect as GSH, might act via a different mechanism than GSH. Since glutamate can bind to both AMPA and kainate receptors, its action is probably mediated via NMDA, AMPA and kainate receptors. The results obtained supported that both NMDA and AMPA had sedative effects. The NMDA receptor usually coexists with the AMPA receptor in the postsynaptic membrane (Nadler 2007). On the other hand, DHPG had no effect in this study, and GSH has no action on the mGluRs (Wang et al. 2006). Thus, it appears likely that the hypnotic and sedative effects of glutamate are induced by interaction with NMDA and AMPA receptors. However, the activity of group II mGluRs regulates the HPA axis (Scaccianoce et al. 2003), and group III mGluRs agonists have anxiolytic- and antidepressant-like effects in rats (Pałucha et al. 2004). Therefore, it is necessary to further investigation the interaction between mGluRs and stress behavior.

In conclusion, the central administration of glutamate attenuates stress-induced behaviors and triggers sleep-like behavior in neonatal chicks. Furthermore, it was demonstrated that NMDA and AMPA, but not kainate and DHPG, also have a sedative effect. It is suggested that glutamate-induced hypnosis and sedation may be necessary for the interaction between NMDA and AMPA receptors. Therefore, further investigation, for example co-administration with NMDA or AMPA antagonists, is needed for a better understanding the mechanism of glutamate. In addition, whether or not NMDA and AMPA having a sedative effect have an antianxiety effect should be confirmed in future.

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