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TWO RECEPTORS ARE INVOLVED IN THE CENTRAL FUNCTIONS OF KYNURENIC ACID UNDER AN ACUTE STRESS IN NEONATAL CHICKS

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Abstract—Intracerebroventricular (i.c.v.) injection of kynurenic acid (KYNA) had sedative and hypnotic effects during stress in neonatal chicks. However, its mechanism has not been clarified. KYNA is an endogenous antagonist of the α7 nicotinic acetylcholine (α7nACh) receptor and N-methyl-D-aspartate (NMDA) receptor. Therefore, this study clarified the mechanism of sedative and hypnotic effects of KYNA in the brain during an acute stress. In Experiment 1, to investigate the relationship between KYNA and the α7nACh receptor, KYNA was injected i.c.v. with galantamine, an agonist of the allosteric potentiating site of the α7nACh receptor. Galantamine did not attenuate the effect of KYNA, but higher levels of galantamine caused harmful effects. In Experiment 2, the role of the NMDA receptor was investigated using the NMDA receptor antagonist (+)-MK-801, D-serine which has high affinity to a co-agonist glycine site at the NMDA receptors, NMDA as the NMDA receptor agonist, and 2,3-pyridinedicarboxylic acid (QUIN), an agonist of the NMDA receptor subgroup containing the subunits NR2A and NR2B. The behavioral changes following KYNA were partially attenuated by QUIN alone. In conclusion, we suggest that KYNA functioned via the simultaneous inhibition of the α7nACh receptor and NMDA receptor subgroup containing the subunits NR2A and NR2B.

Key words: stress, kynurenic acid, α7nACh receptor, NMDA receptors, chick.

INTRODUCTION

Kynurenic acid (KYNA) is one of the tryptophan (TRP) metabolites in the kynurenine (KYN) pathway (Stone, 2001). KYNA is present in the mammalian brain in low (rodents) to high (human) nanomolar concentrations, and is an endogenous antagonist of two receptors that are closely linked to cognition and psychosis, i.e. the α7 nicotinic acetylcholine (α7nACh) receptor (Hilmas et al., 2001) and the N-methyl-D-aspartate (NMDA) receptor (Kessler et al., 1989). Two nACh receptor subtypes are found in abundance in the mammalian central nervous system. One binds nicotine with high affinity and is composed of α4 and β2 subunits; the other binds α-bungarotoxin and is most probably a homomeric α7nACh receptor (Lindstrom, 1997). KYNA, a non-competitive blocker for the presynaptic α7nACh receptor (Hilmas et al., 2001), regulates glutamate release and acts as a competitive antagonist of several types of glutamate receptors with a particularly high affinity to the strychnine-resistant glycine-co-agonist site of the NMDA receptor (Füvesi et al., 2012).

In previous studies, intracerebroventricular (i.c.v.) injection of some amino acids caused sedative and hypnotic effects under an acute stressful condition. For instance, L-proline induced sedative and hypnotic effects acting at the NMDA receptor (Hamasu et al., 2010), as did L-serine (Shigemi et al., 2008) and L-ornithine (Kurata et al., 2011) acting through a gamma aminobutyric acid A ($GABA_A$) receptor under a social isolation stress. We also found that i.c.v. injection of KYNA induced sedative and hypnotic effects in neonatal chicks (Yoshida et al., 2012), but the precise mechanism has not been studied. Therefore, this study investigates the mechanism of sedative and hypnotic effects of KYNA in the brain under an acute stress. As described above, because KYNA may be associated with two primary receptors, we examined the relationships between the function of KYNA and the α7nACh receptor in Experiment 1 and the NMDA receptor in Experiment 2.

In Experiment 1, galantamine hydrobromide, with modification of the levels applied by Wu et al. (2007), was used to investigate the role of the α7nACh receptor. Galantamine is a nicotinic allosteric potentiating ligand effectively increasing α7nACh receptor activation at sub-saturating agonist concentrations (Pereira et al., 2002). Additionally, galantamine is a weak reversible cholinesterase inhibitor. However, its nicotinic allosteric potentiating ligand action seems to be an important determinant of its clinical effectiveness (Lopes et al., 2007). Acting primarily as a nicotinic allosteric potentiating ligand, galantamine improves synaptic transmission and decreases neurodegeneration, two effects essential for its cognition-enhancing properties (Santos et al., 2002; Dajas-Bailador et al., 2003; Arias et al., 2004; Kihara et al., 2004; Zhang et al., 2004).

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Abbreviations: α7nACh, α7 nicotinic acetylcholine; ANOVA, analysis of variance; KYNA, kynurenic acid; NMDA, N-methyl-D-aspartate; QUIN, 2,3-pyridinedicarboxylic acid; TRP, tryptophan.

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In addition to the α7nACh receptor, the NMDA receptor may also be involved in the function of KYNA since KYNA antagonizes the response to NMDA via an action at the strychnine-insensitive glycine receptor (Birch et al., 1988). Accordingly, in Experiment 2, we administered a variety of agonists or antagonists to the NMDA receptor to further investigate the mechanism of KYNA in the chick brain. Four pharmacological reagents were used including (+)-MK-801, D-serine, NMDA, and 2,3-pyridinedicarboxylic acid (QUIN). KYNA was co-injected with (+)-MK-801 (Hamasu et al., 2010), a NMDA receptor antagonist. While KYNA is a confirmed antagonist of the NMDA receptor in mammals, it had to be confirmed that KYNA acts as an agonist of the NMDA receptor in chicks. This idea came from the fact that i.c.v. injection of NMDA had a similar effect in chicks to that induced by KYNA (Yamane et al., 2009b). Secondly, we co-administered KYNA with D-serine (Danysz and Parsons, 1998) to confirm KYNA antagonized at the glycine site on the NMDA receptors, since D-serine has high affinity to a co-agonist glycine site at the NMDA receptors. Third, KYNA was co-administered with NMDA (Yamane et al., 2009b) to determine if KYNA has an agonist or antagonistic effect compared to NMDA. Finally, KYNA was co-administered with QUIN to confirm the contribution of NMDA receptor subgroup, since QUIN acts as the agonist of the NMDA receptor subgroup containing the subunits NR2A and NR2B (de Carvalho et al., 1996; Brown et al., 1998).

EXPERIMENTAL PROCEDURES

Animals

One-day-old male layer 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. Food (AX, Toyohashi Feed and Mills Co., Ltd., Aichi, Japan) and water were freely accessible. Chicks were reared in a group (20–25 per cage) until the start of the experiment. On the day of the experiment, chicks (5 days old) were assigned to treatment groups based on their body weight in order to produce uniform treatment groups, and the number of animals used in each group was kept to a minimum while still ensuring adequate statistical power. Experimental procedures followed the guide for animal experiments of the Faculty of Agriculture, the Graduate Course of the Kyushu University, as well as the Law (No. 105) and Notification (No. 6) of the Government.

Preparation of drugs

KYNA and NMDA were purchased from Sigma (St. Louis, MO, USA). Galantamine hydrobromide, D-serine, and QUIN were purchased from Wako (Osaka, Japan) and (+)-MK-801 maleate was purchased from Funakoshi (Tokyo, Japan). Drugs were dissolved in 0.85% saline containing 0.1% Evans Blue. In Experiments 1 and 2, the negative control group was given the saline solution mentioned above and the positive control was injected with KYNA alone.

I.c.v injection and experimental design

The i.c.v. injections were made using a microsyringe according to the method of Davis et al. (1979) and Koutoku et al. (2005). The stress and pain associated with this method are minimal, as described elsewhere (Koutoku et al., 2005). The injected volume was 10 μl. In Experiment 1, chicks were injected i.c.v. with either saline, KYNA (100 nmol) or KYNA (100 nmol) plus galantamine hydrobromide (0.25, 0.5, or 1 μmol). The dose of galantamine hydrobromide was modified from the doses reported by Wu et al. (2007). In Experiment 2, chicks were injected i.c.v. with either saline, KYNA (100 nmol), KYNA (100 nmol) plus (+)-MK-801 maleate (0.5 nmol), KYNA (100 nmol) plus D-serine (0.84 μmol), KYNA (100 nmol) plus NMDA (1 nmol) or KYNA (100 nmol) plus QUIN (100 nmol). After 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 water and diet. Chick vocalizations were simultaneously recorded and the number of distress vocalizations was counted using Sound Engine (Coderium Inc., Sapporo, Japan). Video cameras were positioned to record the behavior of chicks from three different directions on DVD. Based on the method reported by van Luijtelaar et al. (1987), chick behaviors were classified into four categories: (1) active wakefulness; (2) standing/sitting motionless with eyes opened; (3) standing motionless with eyes closed; and (4) sitting motionless with drooped head (sleeping posture). In addition, (5) an abnormal posture was added in Experiment 1. The monitoring systems were set in a separate room to avoid disturbing the animals as reported by Yamane et al. (2009a). At the conclusion of the experiments, the birds were decapitated following anesthetization with isoflurane (Mylan Inc., Tokyo, Japan). The brains were removed and the location of the Evans Blue dye was confirmed. Data from chicks without dye in the lateral ventricle were excluded from the analysis.

Statistical analysis

In all experiments, data were statistically analyzed by one-way analysis of variance (ANOVA). When significant ($P < 0.05$) effects were detected, the Tukey–Kramer test was used as a post hoc test. Data were analyzed using StatView Version 5.0 software (SAS Institute, Cary, NC, USA). Values are presented as means ± standard error of mean (SEM). All data were first subjected to the Thompson rejection test to eliminate outliers ($P < 0.01$), after which the remaining data were used.

RESULTS

Experiment 1: Effects of i.c.v. injection of KYNA and galantamine on social isolation-induced behaviors in chicks

Fig. 1a shows the effect of i.c.v. injection of KYNA and KYNA plus several doses of galantamine on distress

vocalizations during the 10-min isolation-induced stress. KYNA significantly ($F(4,30) = 4.143$, $P < 0.05$) reduced distress vocalizations compared to the control, and co-injection of galantamine (0.25, 0.5, and 1 μmol) did not attenuate this effect. Fig. 1b shows the effect of i.c.v. injection of KYNA and KYNA plus several doses of galantamine on spontaneous activity during 10-min isolation-induced stress. No significant ($F(4,30) = 0.636$, $P > 0.05$) effect was detected on the spontaneous activity among treatments. Table 1 shows the effect of i.c.v. injection of KYNA and several doses of galantamine on various behaviors in chicks in response to social separation stress for 10 min. KYNA significantly ($F(4,30) = 3.976$, $P < 0.05$) reduced the time spent in active wakefulness compared to the control, and galantamine dose-dependently attenuated the effect of KYNA. In standing/sitting motionless with eyes open, significant ($F(4,30) = 2.732$, $P < 0.05$) effects of treatments were detected. KYNA tended to decrease the value, but 0.5 μmol of galantamine reversed this effect of KYNA. No significant ($F(4,30) = 1.000$, $P > 0.05$) effect was observed in standing motionless with eyes closed. KYNA significantly ($F(4,30) = 19.875$, $P < 0.0001$) increased the time spent in the sleeping posture compared to the control, and galantamine attenuated the effect of KYNA in a dose-dependent manner. In addition, abnormal behavior ($F(4,30) = 5.058$, $P < 0.005$) was observed in KYNA plus galantamine (0.5 and 1 μmol) in which chicks spread their legs and extended their wings, differing from the sleeping posture.

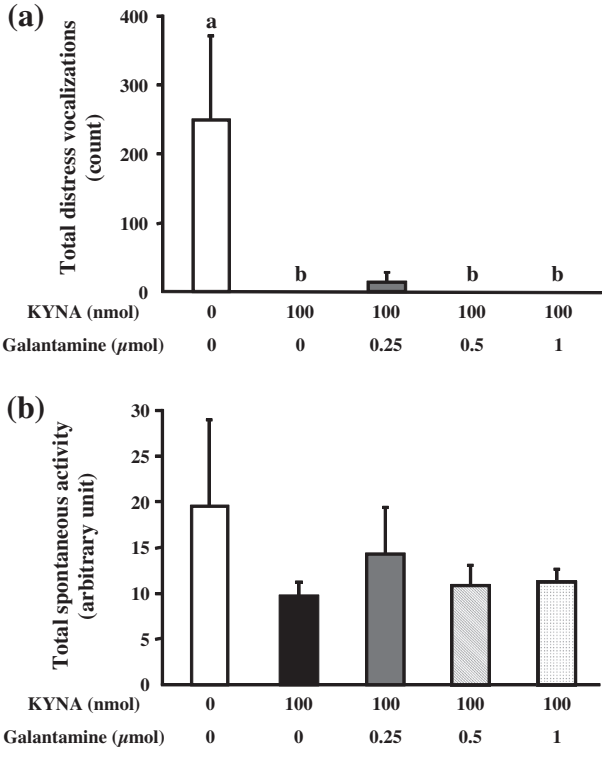

Fig. 1. Effect of i.c.v. injection of saline, kynurenic acid (KYNA), KYNA plus several doses of galantamine on (a) total distress vocalizations and (b) total spontaneous activity during 10 min of isolation in 5-day-old layer chicks. Results are expressed as means ± SEM. The number of chicks used in each group was seven.

Experiment 2: Effects of i.c.v. injection of KYNA, (+)-MK-801, D-serine, NMDA, and QUIN on social isolation-induced behaviors in chicks

Fig. 2 shows the effect of i.c.v. injection of saline, KYNA, KYNA plus (+)-MK-801, D-serine, NMDA, and QUIN on total spontaneous activity during a 10-min social isolation stress. KYNA significantly ($F(5,30) = 4.266$, $P < 0.005$) decreased spontaneous activity compared to saline, and co-injection of (+)-MK-801, D-serine, and NMDA did not modify the effect of KYNA. The effect of KYNA was partially attenuated by QUIN. Table 2 shows the effect of i.c.v. injection of saline, KYNA, KYNA plus (+)-MK-801, D-serine, NMDA, and QUIN on various behaviors of chicks in response to social separation stress for 10 min. Significant effects were detected in the time spent in active wakefulness ($F(5,30) = 6.555$, $P < 0.0005$), standing/sitting motionless with eyes open ($F(5,30) = 3.567$, $P < 0.05$), and the sleeping posture ($F(5,30) = 25.385$, $P < 0.0001$). KYNA significantly decreased the time spent in active wakefulness compared to saline, but (+)-MK-801, D-serine, and NMDA did not alter the effect of KYNA. In standing/sitting motionless with the eyes open, KYNA mildly, but not significantly, increased the time spent in this posture. (+)-MK-801 tended to inhibit and NMDA did not modify the effect of KYNA. Both D-serine and QUIN tended to enhance the effect of KYNA. There was no effect ($F(5,30) = 0.502$, $P > 0.05$) on standing motionless with eyes closed. No distress vocalizations were found in some groups. While vocalizations were not counted, changes in vocalization frequencies were

Table 1. Effect of i.c.v. injection of kynurenic acid (KYNA) and galantamine on various behavioral categories of 5-day-old layer chicks in response to social separation stress for 10 min[1]

KYNA (nmol)	0	100	100	100	100
Galantamine (μmol)	0	0	0.25	0.5	1
Active wakefulness	229 ± 88^{a}	0 ± 0^{b}	6 ± 4^{b}	23 ± 15^{b}	97 ± 61^{ab}
Standing/sitting motionless with eyes open	279 ± 67 ^{ab}	160 ± 21^{b}	353 ± 71^{ab}	439 ± 75^{a}	229 ± 76^{ab}
Standing motionless with eyes closed	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Sitting motionless with drooped head (sleeping posture)	91 ± 45^{bc}	440 ± 21^{a}	241 ± 71^{b}	39 ± 18^{c}	10 ± 12^{c}
Abnormal behavior	0 ± 0^{b}	0 ± 0^{b}	0 ± 0^{b}	98 ± 64^{ab}	265 ± 96^{a}
Total	600	600	600	600	600

[1] Values are means ± SEM in seconds. The number of chicks used in each group was seven. Groups with different letters are significantly different ($P < 0.05$).

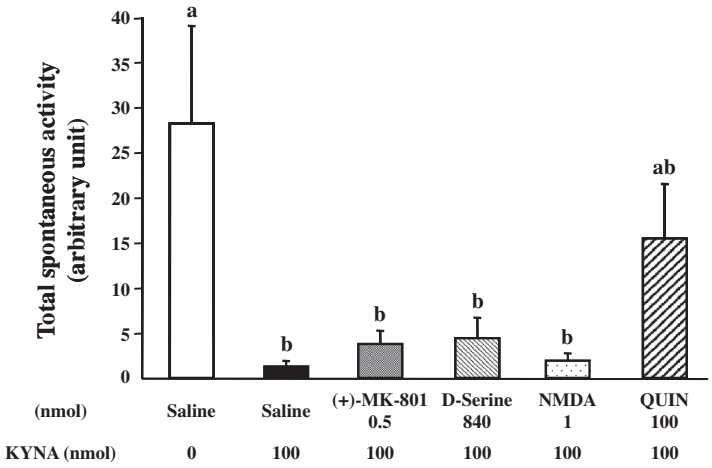

Fig. 2. Effect of i.c.v. injection of saline, kynurenic acid (KYNA), KYNA plus (+)-MK-801, D-serine, N-methyl-D-aspartic acid (NMDA), and 2,3-pyridine dicarboxylic acid (QUIN) on total spontaneous activity during 10 min of isolation in 5-day-old layer chicks. Results are expressed as means ± SEM. The number of chicks used in each group was six. Groups with different letters are significantly different ($P < 0.05$).

Table 2. Effect of i.c.v. injection of kynurenic acid (KYNA) with or without (+)-MK-801, D-serine, N-methyl-D-aspartic acid (NMDA), and 2,3-pyridine dicarboxylic acid (QUIN) on various behavioral categories of 5-day-old layer chicks in response to social separation stress for 10 min[1]

KYNA (nmol) Drug (nmol)	0 Saline	100 Saline	100 (+)-MK-801 0.5	100 D-Serine 840	100 NMDA 1	100 QUIN 100
Active wakefulness	383 ± 95^{a}	72 ± 33^{b}	4 ± 4^{b}	103 ± 66^{b}	118 ± 24^{b}	217 ± 37^{ab}
Standing/sitting motionless with eyes open	171 ± 69^{ab}	264 ± 46^{ab}	156 ± 22^{b}	357 ± 50^{ab}	243 ± 57^{ab}	379 ± 33^{a}
Standing motionless with eyes closed	0 ± 0	17 ± 17	5 ± 5	14 ± 14	10 ± 10	0 ± 0
Sitting motionless with drooped head (sleeping posture)	46 ± 31^{c}	246 ± 27^{b}	434 ± 26^{a}	126 ± 37^{bc}	229 ± 45^{b}	4 ± 4^{c}
Total	600	600	600	600	600	600

[1] Values are means ± SEM in seconds. The number of chicks used in each group was six. Groups with different letters are significantly different ($P < 0.05$).

recorded. Fig. 3 demonstrates the frequencies of vocalization after i.c.v. administration with saline, KYNA, KYNA plus (+)-MK-801, D-serine, NMDA, and QUIN. Each vocalization consisted of repetitions of a syllable type. The frequency of vocalizations ranged from 2 to 8 kHz following saline, but disappeared after i.c.v. injection of KYNA, KYNA with (+)-MK-801, D-serine, and NMDA. Vocalizations after co-administration of KYNA and QUIN were present, but of lower frequency following injection with saline.

DISCUSSION

In chicks, the ACh receptor plays an important role in the control of isolation stress-induced vocalizations. Non-selective ACh receptor agonists as well as muscarinic and nACh receptor agonists decreased isolation stress-induced vocalizations while antagonists had the opposite effect (Panksepp et al., 1980a,b). Sahley et al. (1981) showed that nicotine attenuated, while the muscarinic antagonist scopolamine increased the frequency of separation-induced distress vocalizations. In Experiment 1, total distress vocalizations were reduced by KYNA, but galantamine did not attenuate the effect of KYNA. This was not the case in behavioral analysis, since decreased active wakefulness and increased sleeping posture by KYNA were dose-dependently attenuated by galantamine. From the results obtained here, it is suggested that a part of the function of KYNA is mediated through inhibition of the α7nACh receptor (Hilmas et al., 2001). The effect of a nicotinic allosteric potentiating ligand may compete with KYNA for the α7nACh receptor. On the other hand, high doses of galantamine induced abnormal behavior in the present study, suggesting that excess stimulation of α7nACh receptor might be harmful to chick behavior. The behavior in which chicks spread their legs and extended their wings has also been observed in a previous study following i.c.v. injection of D-cysteine (Yamane et al., 2009a). However, we could not assert whether this abnormal behavior was caused by galantamine alone or galantamine with KYNA, since there was not a galantamine-only injected group. Nicotine acts as a nACh receptor agonist, and systemic administration of nicotine stimulated the release of dopamine, noradrenaline, serotonin, and glutamate in several brain regions including the prefrontal cortex, striatum, nucleus accumbens, and hippocampus (Janhunen and Ahtee, 2004; Kashkin and De Witte, 2005; Shearman et al., 2008). Similarly, the allosteric

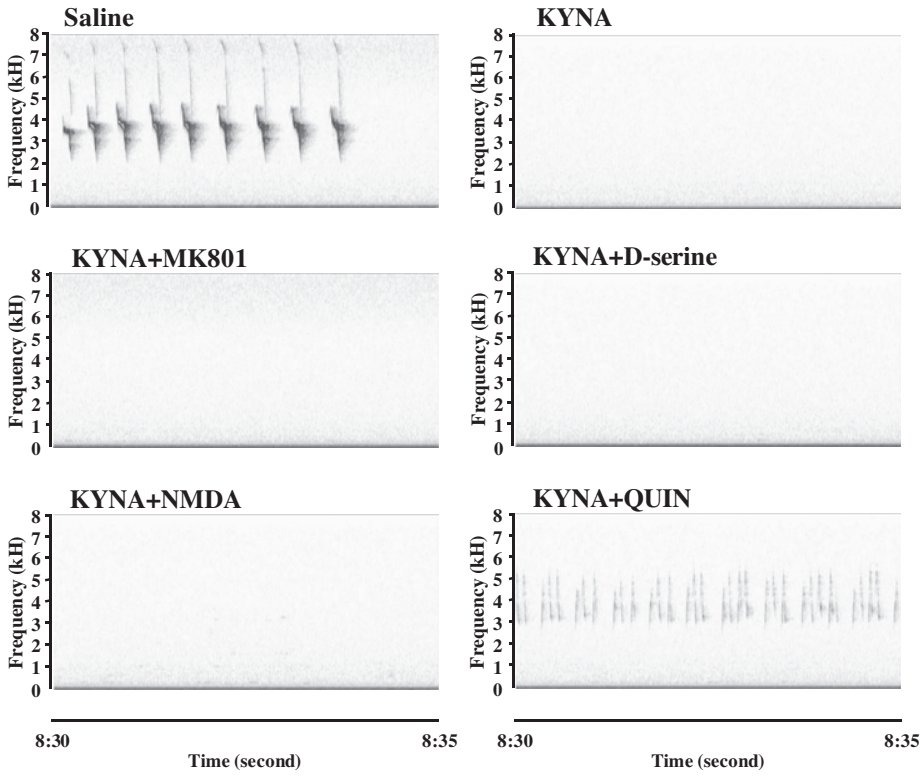

Fig. 3. Effects of i.c.v. injection of saline, kynurenic acid (KYNA), KYNA plus (+)-MK-801, KYNA plus D-serine, KYNA plus N-methyl-D-aspartic acid (NMDA), and KYNA plus 2,3-pyridine dicarboxylic acid (QUIN) on frequency of the vocalization during 10 min of isolation in 5-day-old layer chicks. The number of chicks used in each group was six.

modulating action of galantamine on nACh receptors could enhance the release of these neurotransmitters in the brain (Ago et al., 2011). Future studies should attempt to clarify the mechanism of galantamine in the chick brain using monoamine analysis.

In Experiment 2, KYNA significantly decreased spontaneous activity compared to saline. Similar results were obtained with the behavior of active wakefulness. However, (+)-MK-801, D-serine, and NMDA did not block the effect of KYNA. KYNA significantly increased the time spent in the sleeping posture compared to saline, but co-injection of QUIN attenuated the effect of KYNA. Yamane et al. (2009b) reported that although NMDA induced a sedative effect, the efficacy of NMDA on sleep-like behavior was less than that of glutamate. According to Hamasu et al. (2010), when the NMDA receptor antagonist (+)-MK-801 was co-injected i.c.v. with L-proline, the suppression of stress behavior by L-proline was attenuated. These reports suggest the importance of the NMDA receptor in the attenuation of stress-induced behavior. In the present study, (+)-MK-801 was used as an NMDA receptor antagonist, even though KYNA is confirmed as an NMDA receptor antagonist in mammals. This is done to determine if KYNA was acting more like an NMDA antagonist (i.e. (+)-MK-801) or an NMDA agonist since i.c.v. injection of NMDA had an effect similar to KYNA (Yamane et al., 2009b). However, neither (+)-MK-801 nor NMDA modified the behavior induced by KYNA. At the sub-receptor sites, D-serine acts as an endogenous ligand for an NMDA receptor-related glycine site (Hashimoto and Oka, 1997). Asechi et al. (2006) observed that D-serine did not have sedative and hypnotic effects as observed with L-serine in chicks. Thus, the fact that KYNA and D-serine did not modify the behavior was expected. Since the behavior following the injection of KYNA alone was similar to that following (+)-MK-801, D-serine, and NMDA, we conclude that they are not involved with KYNA in the brain.

Results for the KYNA plus QUIN treatment were very interesting. QUIN is a weak but specific competitive agonist of the NMDA receptor subgroup containing the subunits NR2A and NR2B (de Carvalho et al., 1996; Brown et al., 1998). We could not count total distress vocalization in KYNA plus QUIN treatment because chicks injected with this combination calmly vocalized. QUIN has a neurotoxic effect while KYNA has a neuroprotective effect (Myint and Kim, 2003; Wichers et al., 2005). From the present results and previous reports, it is suggested that the effect of KYNA was a result of partial inhibition of the NMDA receptor at the level of a subgroup containing the subunits NR2A and NR2B.

Additionally, the result of distress vocalizations in KYNA plus QUIN was similar to the previous study (Zhang et al., 2004) with high doses of serotonin. In both experiments, TRP metabolism, in particular the KYNA or serotonin pathway, is affected. It is suggested that TRP metabolites function to control distress vocalizations in young chicks. In addition, it was

reported that changes in the absolute and relative concentrations of KYNA and QUIN in the brain have been implicated in a great number of neurodegenerative disorders (Robotka et al., 2008). In future studies, it will be important to focus on the relationship of KYNA and QUIN in the chick brain.

CONCLUSION

The function of KYNA was mediated through the simultaneous inhibition of both the α7nACh receptor and NMDA receptor subgroups containing the subunits NR2A and NR2B in chicks under stressful conditions. Li et al. (2012) confirmed the existence of the NR2A–α7nAChR interaction. The results obtained here suggest that KYNA co-administration with galantamine or QUIN might support the NR2A–α7nAChR interaction. The relationships between KYNA and the NR2A–α7nAChR interaction remain to be further clarified.

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