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Glutamatergic Transmission in the Avian Brain: Model for Human Excitotoxicity Disorders Study

(Penghantaran Glutamatergik dalam Otak Burung: Model bagi Kajian Gangguan Keeksitotoksikan Manusia)

M.R. ISLAM, Y. ATOJI & J.M. ABDULLAH*

ABSTRACT

Glutamatergic dysfunction has been suggested as a possible substrate of the pathophysiology of many neurodegenerative diseases, specifically since glutamatergic transmission is severely altered by the early degeneration of cortico-cortical connections and hippocampal projections in Alzheimer's disease, schizophrenia and Huntington's disease in humans. Of the multiple genes, vesicular glutamate transporters, glutamate receptors and excitatory amino acid transporters have a significant role in glutamatergic transmissions. The regional differences of glutamatergic neurons and glutamate receptor neurons suggest many glutamatergic projections in the avian brain. Glutamatergic target areas are expected to show high activity of glutamate transporters that remove the released glutamate from the synaptic clefts. The distribution of the glutamate-related genes indicates that many glutamatergic transmissions exist in the avian brain. This review provide insights of glutamatergic circuits in birds particularly in the pallial organization of glutamatergic neurons and connection with the striatum and hippocampal-septal pathway and comparison with those of mammalian brain which are responsible for Alzheimer's disease, schizophrenia and Huntington's disease in humans.

Keywords: Central nervous system, glutamate receptors, mRNA expression, neurons, vesicular glutamate transporters

ABSTRAK

Disfungsi Glutamatergik telah dicadangkan sebagai substrat patofisiologi yang mungkin untuk penyakit neurodegeneratif, khususnya kerana penghantaran glutamatergik banyak diubah oleh degenerasi awal sambungan kortikal kortiko dan unjuran hipokampal dalam penyakit Alzheimer, skizofrenia dan penyakit Huntington pada manusia. Daripada pelbagai gen yang ada, pembawa glutamat vesikular, reseptor glutamat dan pembawa asid amino berangsang mempunyai peranan penting dalam transmisi glutamatergik. Perbezaan serantau neuron glutamatergik dan neuron reseptor glutamat mencadangkan terdapat banyak unjuran glutamatergik wujud di dalam otak burung. Kawasan sasaran Glutamatergik dijangka menunjukkan aktiviti pengangkutan glutamat yang tinggi bagi membuang glutamat yang dikeluarkan dari celahan sinaptik. Taburan gen yang berkaitan glutamat menunjukkan bahawa banyak penghantaran glutamatergik wujud di dalam otak burung. Ulasan ini menyediakan gambaran tentang litar glutamatergik dalam burung terutamanya dalam organisasi palial neuron glutamatergik dan perkaitan dengan striatum dan laluan septal hipokampal serta perbandingan dengan otak mamalia yang bertanggungjawab bagi penyakit Alzheimer, skizofrenia dan penyakit Huntington pada manusia.

Kata kunci: Neuron; pembawa glutamat vesikular; reseptor glutamat; sistem saraf pusat; ungkapan mRNA

INTRODUCTION

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) (Headley & Grillner 1990) but excessive glutamate in the synaptic cleft produces excitotoxicity in the CNS (Brustovetsky et al. 2004; Obrenovitch & Urenjak 1997). Interruption of glutamatergic circuit is one of the important grounds for glutamate deposit in the synaptic cleft causing excitotoxicity. Excitotoxicity involved in neurodegenerative diseases in the CNS of human such as Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS) as well as spinal cord injury and stroke (Kim et al. 2002).

Vesicular glutamate transporters (VGLUTs) transport and store glutamate into synaptic vesicles at the presynaptic terminals, then the glutamate are released into the synaptic cleft by exocytosis and binds to glutamate receptors (GluRs) on postsynaptic membranes. The excitatory amino acid transporters (EAATs) or high-affinity glutamate transporters play essential roles in removing the released glutamate from the synaptic cleft (Kanai & Hediger 2004). Thus VGLUTs, GluRs and EAATs boast a significant role in glutamatergic transmission (Figure 1) to uncover amenable targets that may contribute to our understanding of glutamate excitotoxicity. Three subtypes of VGLUTs have been identified in mammals and are referred to as VGLUT1, VGLUT2, and VGLUT3 (Aihara et al. 2000; Gras et al. 2002; Ni et al. 1994). VGLUT1 and VGLUT2 mRNAs are expressed in the glutamatergic neurons, whereas the VGLUT3 mRNA is found in other types

of neurons and in the astrocytes (Bai et al. 2001; Gras et al. 2002; Herzog et al. 2004; Takamori 2006). In general, VGLUT1 and VGLUT2 show a complementary expression pattern of the glutamatergic neurons in the mammalian brain; VGLUT1 mRNA is expressed mainly in the cerebral cortex, hippocampus and cerebellar cortex, whereas the greatest expression of VGLUT2 mRNA is seen in the thalamus, hypothalamus, lower brainstem and cerebellar nuclei (Barroso-Chinea et al. 2007; Fremeau et al. 2001; Hisano et al. 2000). Because of VGLUT1 and VGLUT2 are restricted to known glutamatergic neurons, their presence have become a reliable molecular phenotypic marker to identify the glutamatergic neurons (Takamori et al. 2000). Cellular detection of VGLUT2 mRNA is so far the only available and reliable method to label cell bodies of glutamatergic neurons, because VGLUT1 mRNA is not known yet in birds. The postsynaptic actions of glutamate are mediated by at least three major pharmacologically distinct classes of ionotropic receptors at which glutamate modulates the release of intracellular Ca^{2+} as well as metabotropic receptors. The ionotropic receptors contain glutamate-gated cation channels and are named according to their selective agonists as *N*-methyl-D-aspartate (NMDA)-type, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type and kainite-type receptors (Collingridge & Lester 1989). AMPA-type glutamate receptors, which mediate fast excitatory postsynaptic potentials, are assembled as GluR1, GluR2, GluR3 and GluR4 (Keinänen et al. 1990). GluR1–4 subtypes mRNA and proteins are expressed differentially and widely in the neurons of the birds and mammalian CNS (Conti et al. 1994; Keinänen et al. 1990; Islam & Atoji 2008; Ottiger et al. 1995; Sato et al. 1993; Theiss et al. 1998; Toledo et al. 2002; Wada et al. 2004). Five excitatory amino acid transporters have been cloned in mammals: L-glutamate transporter 1 (GLT1) or excitatory amino acid transporter 2 (EAAT2) (Pines et al. 1992), excitatory amino acid carrier 1 (EAAC1) or EAAT3 (Kanai & Hediger 1992); L-glutamate / L-aspertate transporter (GLAST) or EAAT1 (Storck et al. 1992), EAAT4 (Fairman et al. 1995) and EAAT5 (Arriza et al. 1997). In contrast, GLT1 is the only identified glutamate transporter in birds (Atoji & Islam 2009). GLT1 preferentially expresses in the telencephalon, including the olfactory bulb, neocortex, hippocampus and striatum is also present in the cerebellum at lower levels (Atoji & Islam 2009; Berger & Hediger 1998; Danbolt et al. 1992; Lehre et al. 1995; Schmitt et al. 2002). Both the neurons and glial cells exhibit high capacity for glutamate uptake (Genelassvili & Schousboe 1998). The cortico-striatal pathway and hippocampal-septal pathway are shown glutamatergic transmission in mammals (Gerfen 2004; Witter & Amaral 2004). In contrast, the regional differences of glutamatergic neurons and AMPA-type receptor neurons suggest many glutamatergic projections in the avian brain. Glutamatergic target areas are expected to show high activity of glutamate transporters that remove the released glutamate from the synaptic clefts. Thus, the distribution of the glutamate-related genes indicates that many glutamatergic transmissions also exist in the avian brain. This review provide insights of glutamatergic transmission in birds and comparison with those of mammalian brain, particularly in the pallial organization of glutamatergic neurons and connection with the striatum and hippocampal-septal pathway which are responsible for Huntington's disease (HD), Alzheimer's disease and schizophrenia in humans.

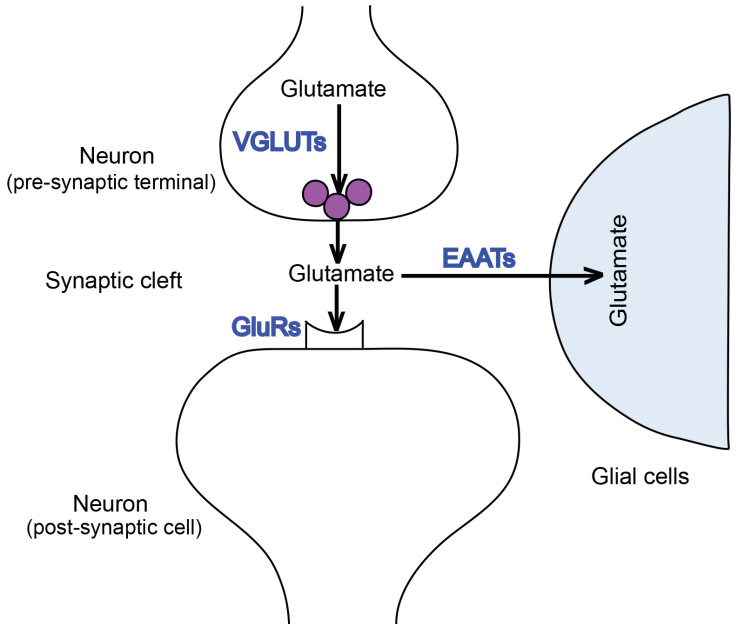

FIGURE 1. Schematic diagram of glutamatergic transmission in mammals is regulated by the vesicular glutamate transporter (VGLUTs), glutamate receptors (GluRs), and excitatory amino acid transporters (EAATs)

HUNTINGTON'S DISEASE AND GLUTAMATERGIC TRANSMISSION

The main hypothesis underlying striatal neurodegeneration in HD has been excitotoxicity (Difiglia 1990). This hypothesis emanated from many studies demonstrating parallels in the effects of excitotoxicity or chemical lesions of the striatum with those observed in HD in patients. In general, excitotoxicity can result from a number of changes, either together or in isolation. These include an increase in release of excitatory neurotransmitters like glutamate and an increase in responsiveness of glutamate receptors (GluRs) either due to an increase in receptor density or number or a change in receptor composition or their signaling properties. Neuronal glutamatergic transmission in both the striatum and cortex are important in the development of the HD phenotype. The corticostriatal pathway is the primary provider of the excitatory glutamatergic inputs into the striatum. The effects of these inputs are regulated by AMPA GluRs receptors on cortico-striatum that function as the gatekeepers of glutamate receive, as well as by the intrinsic membrane properties of medium-sized spiny neurons. When the neurons of this pathway become dysfunctional, excitation of striatal neurons will become abnormal. Furthermore, it is becoming increasingly clear that major morphological alterations in the striatum are probably primed initially by alterations in the intrinsic functional properties of medium-sized spiny neurons (Cepeda et al. 2007). It is thus possible that areas related to these early alterations, such as the limbic system, the cerebral cortex or even the hypothalamus is the initial triggers of changes in motor functions ultimately mediated via the striatum. In fact, it has been speculated that cortical changes are fundamental to the onset and progression of the HD in humans and in mouse models (Cepeda et al. 2007) that can be study by the avian models.

In corticostriatal pathway, the cerebral cortex provides a major input to the striatum. The corticostriatal afferents arise from cortical pyramidal neurons, located primarily in layer V, with layers III and VI. The topographic organization of corticostriatal inputs is well established with the orderly mapping of inputs of regions of the cortex into the topographically related regions of the striatum. Frontal areas provide inputs to the rostral regions of the striatum, sensorimotor cortex provides inputs to the dorso-lateral region and parietal cortex provides inputs to more caudal regions (Gerfen 2004). VGLUT1 mRNA is strongly expressed in layers V and VI, VGLUT2 mRNA is expressed in layers IV and VI of some lobes of the cerebral cortex (Fremeau et al. 2001; Herzog et al. 2004). The immunoreactivity of VGLUT1 and VGLUT2 is intense in the neocortex (Kaneko et al. 2002). In birds, chicken VGLUT2 and VGLUT3 genes have been identified, but the VGLUT1 gene has not been found. Islam and Atoji (2008) reported the sequence of pigeon VGLUT2 cDNA (accession number: FJ428226), whose amino acid shows 99% and 93% identity to the chicken and human VGLUT2, respectively. The previous *in situ* hybridization study and immunohistochemistry demonstrated that VGLUT2 mRNA and protein was distributed in neuronal cell bodies and neuropil, respectively, in the pallium of the telencephalon, many nuclei in the ascending auditory and visual systems and in granule cells of the cerebellar cortex (Atoji 2011; Islam & Atoji 2008). On the other hand, GluR1-4 subtypes mRNA or protein is labeled in neurons of the striatum (Keinänen et al. 1990; Martin et al. 1993; Sato et al. 1993). GLT1 mRNA is expressed in the caudate putamen and globus pallidus in rat brain (Berger & Hediger 1998; Torp 1997). Thus, the glutamatergic neurons inhabit in cortical layers that provide major excitatory input to the striatum. The hyperpallium (apical, interstitial nucleus of the apical, intercalated and densocellular parts of the hyperpallium) of birds and mammalian neocortex appear to derive from the same pallial embryonic subdivision. The adult animals show the typical molecular and cellular features in these structures (Medina 2007). In the avian brain, VGLUT2, GluR1-4 and GLT1 mRNAs expression was also found differentially in the pallium of birds. The principal pallial neurons have excitatory projections to the striatum in birds (Veenman et al. 1995) and in mammals (Broman et al. 2004). The striatum showed the positive expression for AMPA glutamate receptors in birds and mammals (Cornil et al. 2000; Islam & Atoji, 2008; Laverghetta et al. 2006; Ottiger et al. 1995; Sato et al. 1993; Wada et al. 2004). GLT1 mRNA showed positive expression in the glutamatergic terminal fields, i.e., in the striatum of birds (Atoji & Islam 2009). Thus, glutamatergic circuits exist in the pallial-striatal pathway of the avian brain like as mammalian brain.

SCHIZOPHRENIA AND GLUTAMATERGIC TRANSMISSION

The AMPA receptor and VGLUTs are abnormally expressed in schizophrenic brain. AMPA receptor expression is decreased in the medial temporal lobe, hippocampus particularly in the CA3 and CA4 subfields in schizophrenic brain, but there were no differences in the expression of any of the AMPA-associated subunit mRNAs in prefrontal or occipital cortex in schizophrenia (Kerwin et al. 1990; Meador-Woodruff & Healy 2000). While Noga et al. (1997) reported increased AMPA binding in caudate, putamen and accumbens in schizophrenic brain. VGLUT2 mRNA expression was increased in the thalamus in schizophrenia patents, whereas VGLUT1 mRNA expression was decreased (Eastwood et al. 2005; Smith et al. 2001).

ALZHEIMER'S DISEASE AND GLUTAMATERGIC TRANSMISSION

Alzheimer's disease, the leading cause of senile dementia, is characterized by the dysfunction and degeneration of select populations of vulnerable neurons in the hippocampus and other cortical brain regions. In previous studies, it was suggested that such selective neuronal vulnerability may arise through the differential expression of glutamate receptors, the activation of which would lead to signal transduction alterations (McShea et al. 1999; Perry et al. 1999; Zhu et al. 2001). Although it is still

not clear which receptor or receptor classes are involved in these signal transduction alterations in Alzheimer's disease, the glutamate receptor (GluR) family is likely to play a pivotal role. Indeed, previous reports support this notion and glutamatergic transmission is severely altered by early degeneration of corticocortical connections and hippocampal projections in Alzheimer's disease (Francis et al. 1993). These studies support the hypothesis of abnormal glutamatergic neurotransmission in Alzheimer's disease and schizophrenia that involves the ionotropic GluRs in particular. These findings suggest that novel strategies that permit the modulation of these receptors may prove to be of therapeutic utility in these illnesses.

In mammals, dentate gyrus has mossy fiber projection to the CA3 field of the hippocampus and the septal nuclei have projection to the dentate gyrus (Witter & Amaral 2004). Granule cells in the dentate gyrus and pyramidal cells in the Ammon's horn contain glutamatergic neurons (Fremeau et al. 2001; Kaneko et al. 2002). GluR1–3 mRNA is strongly expressed in the pyramidal cells of the Ammon's horn, including CA3, which receives the mossy fibers from granule cells of the dentate gyrus (Keinänen et al. 1990; Sato et al. 1993). Ammon's horn, which projects one of the main efferents to the lateral septal nucleus, is highly enriched in GluR1–3 immunoreactivity as well as in VGLUT1 mRNA (Fremeau et al. 2001; Martin et al. 1993; Rogers et al. 1991). Moreover, the lateral septal nucleus shows intense immunoreactivity for GluR1–3, especially on somata and dendrites (Martin et al. 1993; Rogers et al. 1991). These findings indicate that glutamatergic granule cells in the dentate gyrus give rise to intrahippocampal projections to pyramidal cells in CA3 and in turn, glutamatergic pyramidal cells in the Ammon's horn project extrahippocampal efferents to the lateral septal nucleus. The avian hippocampal formation consists of seven subdivisions; among of them, the V-shaped layer, the triangular and dorsomedial regions are comparable with the dentate gyrus and Ammon's horn, respectively, based on fiber connections with the septum (Atoji & Wild 2004; Atoji et al. 2006). Neurons in the V-shaped layer form intrinsic circuits to the triangular and dorsomedial regions and neurons in the triangular and dorsomedial regions project to the lateral septal nucleus. VGLUT2 mRNA expresses in neurons of the V-shaped layer and of the triangular and dorsomedial regions, and GluR1-4 mRNAs expression and protein localization are found in neurons of the triangular and dorsomedial regions and in the lateral septal nucleus (Islam & Atoji 2008; Ottiger et al. 1995; Wada et al. 2004). GLT1 mRNA is identified in the glial cells throughout the hippocampal formation and the septum (Atoji & Islam 2009). Therefore, it seems to believe that glutamatergic circuits dwell in hippocampal-septal connection in birds.

In conclusion, this review emphasizes the morphological distribution of glutamate-related genes – VGLUTs, GluRs and GLT1 contribute to our understanding of glutamatergic transmission as exhibited in corticostriatal pathway, hippocampal-septal pathway and other relevant areas of the avian brain. Furthermore, glutamatergic circuits will provide the morphological basis for physiological and pharmacological experiments using birds as the potential animal models to elucidate further the underlying mechanisms that underlie glutamatergic transmission both in health as well as in excitotoxic neurodegenerative diseases.

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M.R. Islam & J.M. Abdullah*
Department of Neurosciences, School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan
Malaysia

M.R. Islam
Department of Anatomy and Histology
Bangladesh Agricultural University
Mymensingh-2202
Bangladesh

Y. Atoji
Laboratory of Veterinary Anatomy
Faculty of Applied Biological Sciences
Gifu University, Gifu 501-1193
Japan

*Corresponding author: email: brainsciences@gmail.com

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