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Mini Review

A Brief View of the Central Nervous System with a Focus on Synaptic and Extrasynaptic Transmission

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Abstract

Information transmission in the central nervous system (CNS) is usually thought to consist of a network neurons connected by excitatory and inhibitory synapses. It has been, however, also known the existence of receptors at the extrasynaptic position and non-synaptic release of neurotransmitters and the importance of the role of extrasynaptic signalling has become gradually apparent in recent years. Receptors used in extrasynaptic transmission are mainly metabotropic types except GABAA and NMDA receptors and usually cause slow but lasting effects. Extrasynaptic information transmission modifies the efficiency of the synaptic transmission, regulates excitability in certain areas of the CNS and participates in exchanging information with non-neuronal cells. It has been shown to be involved in long-term potentiation and long-term depression, and also in the formation of neural networks during development. Many of the CNS toxicants and therapeutics are thought to work through extrasynaptic receptors. Neurological disorders such as autism and Alzheimer's disease have also been known to be linked to extrasynaptic signalling. The elucidation of the function of extrasynaptic signalling systems will become increasingly important.

Keywords: *Tonic Modulator; Volume Transmission; Metabotropic Receptor; NMDA Receptor; GABAA Receptor*

Introduction

Although synaptic transmission is a standard method of neural communication, extrasynaptic receptors are known to exist and play an important role in central nervous system (CNS). While synaptic transmission is rapid without cross-talk, extrasynaptic transmission tends to be slow but can affect many at a time. Synaptic transmission allows us to perform highly sophisticated tasks and has been studied as the main object of neuroscientific research. These days, however, the importance of the role of extrasynaptic transmission in modifying the synaptic transmission system has been recognized, and the role of extrasynaptic transmission in the pathology and disease treatment has been of interest and also detailed reviews by experts have been written [1-3]. In this mini-review, CNS function is considered, focusing on synaptic and extrasynaptic transmission, as an information processing system.

Information transmission in organism

Cells have various receptors on the cell membrane to obtain information about the external environment and to exchange information between cells.

It is known that even in unicellular organisms, chemoreceptors play an important role in the ingestion of food and in the avoidance of harmful substances. Some prototypes of receptors of advanced organism, such as Ach muscarinic receptors, can be seen in unicellular organisms [4].

In multicellular organisms, close communication between cells is essential to allow the whole organism to cooperate, and neuronal cells and the synaptic connections are believed to have evolved as a specialized means of transmitting information.

Strangely, peptides are used as the main neurotransmitters in the scattered nervous system of hydra, which is the representative of the organism that appears to have shown the first development of the nervous system with a primitive form of CNS [5]. As more advanced organisms, nematodes such as Caenorhabditis elegans, show almost all types of neural transmission observed in the human CNS, although strangely lacking action potentials [6,7].

Central nervous system

In the CNS of vertebrates including humans, glutamate is used as the main excitatory neurotransmitter for the rapid signal transmission, with ionotropic receptors, causing excitatory postsynaptic potentials that subsequently generate action potentials.

The excitatory network alone causes an excessive uncontrolled activity of the circuit and, therefore, requires inhibitory intervention. GABA and glycine are inhibitory transmitters in the human CNS and released from GABAergic and glycinergic neurons causing inhibitory synaptic potentials through Cl^- channel coupled receptors, suppressing the generation of action potentials in postsynaptic neurons.

In the CNS, there are other partial systems with different neurotransmitters such as dopamine, noradrenaline, serotonin and acetylcholine, which are thought to regulate the activity of the main glutamine-based circuit.

Interestingly, the output neurons that leave the CNS, both the spinal motor neurons and the autonomic pre-ganglionic neurons, are all cholinergic.

Receptors

There are two main types of neurotransmitter receptors: ionotropic and metabotropic. While ionotropic receptors rapidly transmit information by opening directly coupled ion channels and generate excitatory or inhibitory postsynaptic potentials, metabotropic receptors act on the intracellular metabolic system through G proteins to alter the neuron excitability or other properties, with considerable delay and duration. Therefore, synaptic transmission, the main path of information, tends to use mainly ionotropic receptors, and extrasynaptic transmission, the modulating mechanism, tends to use mainly metabotropic receptors [8-10].

Main neural transmissions in CNS

Interestingly, while almost all of terminals of glutaminergic neurons and GABAergic neurons are known to form synapses, the extrasynaptic receptors for glutamate and GABA are known to exist aboundantry [1]. These extrasynaptic receptors are therefore thought to be activated by spilt over transmitters released by synapses or controlled by agonists in other extracellular fluid environments.

In neuromodulatory systems such as norepinephrine, dopamine, serotonin and cholinergic systems, in addition to the glutamatergic and GABAergic systems, the transmitters are often released by axonal varices, most of which do not establish any synaptic contact [2].

Other information transmission systems

The endocrine system plays an important role in the signalling system of multicellular organisms along with the nervous system. In the nervous system, the destination of the information transmission is fixed, but in the endocrine system, the information transmission is substantially directed to the whole body and the information is selected based on the characteristics of the receptor on the receiving side.

In case of autacoids or local hormones, the target will be limited to relatively close areas rather than the whole body.

In other systems, there are various mechanisms for transmitting information between cells such as cytokines, tropic factors and adhesion factors.

Extrasynaptic transmission

Though the neural network in the CNS is composed of excitatory and inhibitory synaptic connections and has been held responsible for the advanced information processing functions of the brain, It has been shown that the interaction of extrasynaptic receptors with their agonists and antagonists in the extracellular fluid, or cerebrospinal fluid, has been shown to have important implications for brain function.

Extrasynaptic receptors are, in a broad sense, all receptors except in the synaptic cleft and extrasynaptic transmission is the information transmission through those receptors.

The term volume transmission was proposed by Agnati., *et al* [11]. They called transmission through the synapse a wiring transmission and transmission through the extracellular space by diffusion a volume transmission. Many experts have adopted that term, and some use non-synaptic transmission almost same meaning [1], though, in this review we use extrasynaptic transmission in the broad sense instead.

Extrasynaptic transmissions have been shown to be involved in the regulation of synaptic function even in nematodes [12].

Numerous examples of the functions performed by extrasynaptic receptors are known. The role of synaptic regulation around synapses is relatively widespread. For example, GABAB receptors suppress the release of neurotransmitters before synapses, and suppress the influx of Ca^{2+} from NMDA receptors after synapses [13].

Types of extrasynaptic transmission

Conceptually, extrasynaptic transmission can classify roughly three types (Figure 1). three types. One is the "perisynaptic modulation" (Figure 1B) in which the receptors are localized perisynaptically and modify the function of the synapse or of the presynaptic and postsynaptic neurons. This includes autoregulation of synaptic transmitter release by presynaptic receptors, long term potentiation, long term depression and also induced neural deaths. The second is "neighbour transmission" (Figure 1C), which transmit information to target cells scattered around. Transmission from varicosities without synapses is typical of this type. The third is "tonic modulation" (Figure 1C). This type of extrasynaptic transmission in the CNS is similar to the endocrine system. In fact, certain types of hormones, oxytocin and vasopressin, for instance, secreted from hypothalamic supraventricular neurons both throughout body through the pituitary and also directly into the cerebrospinal fluid space [14].

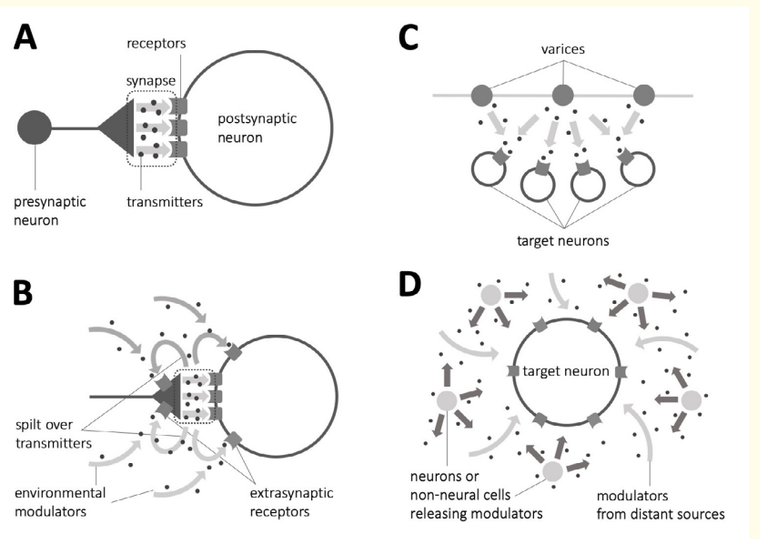

Figure 1: *Synaptic (A) and extrasynaptic (B, C, D) transmissions (conceptual schema).*

A: Synaptic transmission. The information is transmitted from the presynaptic neuron to the postsynaptic neuron in one-to-one fashion.

B: Peri-synaptic modulation. The receptors in the peri-synaptic sites of the pre-and post-synaptic neurons are stimulated by spilt over transmitters from synapse and/or extrasynaptically released modulators, modifying synaptic function and/or characters of pre- and post-synaptic neurons.

C: Neighbour transmission. As at the varices, released transmitters stimulate multiple targets around one-to-many fashion.

D: Tonic modulation. Extrasynaptic receptors are stimulated by environmental modulators released by multiple neurons and/or non-neural cells around or from distant sites.

Needless to say, there are actually many types of receptors and transmitters (or modulators), although each indicated by one type of symbol here. The action can be positive or negative depending on the combination of transmitters and receptors.

NMDA receptors in extrasynaptic transmission

The NMDA receptor is an ionotropic receptor and is known to be present in many extrasynaptic sites. A unique feature of the NMDA receptor is that when activated, it can pass Ca^{2+} to increase the intracellular Ca^{2+} concentration, causing relatively long lasting changes in neurons, similar to the metabotropic receptors. While the calcium influx through NMDA receptors is believed to be involved in long-term potentiation of the hippocampus, the excessive Ca^{2+} influx causes cell death by inducing autolysis. Extrasynaptic, rather than synaptic, NMDA receptors are believed to have strong cytotoxicity and related to neurological diseases [15,16], and it has been reported in connection with Alzheimer's disease that extrasynaptic NMDA receptors, but not synaptic NMDA receptors, are closely involved in τ protein-dependent cytotoxicity [17,18].

GABAA receptors in extrasynaptic transmission

It is interesting to see how neural networks are formed in the developing brain. Ben-Ari and colleagues showed that in the developing brain GABA acts as excitatory transmitter and causes periodic spontaneous depolarizations (GDPs) of hippocampal pyramidal neurons, which are, they suggested, necessary for the normal formation of the neural network [19]. GDPs appear already before the synapse formation and it is speculated that the extrasynaptic GABAA receptors can generate GDPs without established synaptic connections [20].

The role of the extrasynaptic GABAA receptor in development has been studied extensively in recent years. There is a question about the polarity of the response with respect to the GABA tone regulation: excitatory or inhibitory. The GABAA receptors act as Cl^- channels, but during development, neuronal intracellular Cl^- concentrations are relatively high and when chloride channels open, the negative Cl^- efflux causes depolarization. The intracellular Cl^- concentration gradually decreases with the developmental stage and the action of GABA becomes completely inhibitory in adults. The regulation of the intracellular Cl^- concentration is achieved mainly by two enzymes: KCC2 pumps out and NKCC1 pumps in chloride ions [21].

Oxytocin has the effect of reducing the intracellular Cl^- concentration and converting the effects of GABA into inhibitory. Tyzio and colleagues found that brain oxytocin levels increased rapidly at birth in mouse, suggesting that it could act to reduce stress on the brain during delivery [22]. Leonzino M., *et al.* argued that the action of oxytocin is also important during long developmental stages and its imperfections can lead to developmental disorders such as autism [23]. Deterioration of Excitatory/Inhibitory balance in the brain is believed to be involved in various stages before and after birth with the onset and pathology of autism [24,25]. For treatment, to regulate tonic modulation mediated by GABAA receptors, administration of oxytocin or bumetanide, which reduces the concentration of intracellular chloride ions, was attempted with some beneficial effects [26,27].

Glycine in extrasynaptic transmission

Glycine is an inhibitory transmitter similar to GABA, it mainly works in the brainstem and spinal cord in adults, but not in the upper brain. Transient expression of strychnin-sensitive glycine receptors was, however, found in hippocampal pyramidal cells of neonatal rats [28] and their presence has been also confirmed histologically without evident existence of synapses, indicating working as extrasynaptic transmission. Since glycine receptors are Cl^- channels like the GABAA receptors, glycine is thought to exert its effect by tonic excitatory or inhibitory modulation depending on the intracellular Cl^- concentration during development and in adult [29,30].

Intrinsic agonists of extrasynaptic transmission

There is an important question about extrasynaptic transmission, especially the tonic type. It is what is the natural intrinsic modulator of receptors. GABAA receptors are known to have significant affinities for taurine and beta-alanine. Kilb and Fukuda discussed the role of taurine in brain development [31], but β-alanine has a significant affinity for BABAA receptors and has been also suggested as an endogenous agonist [32].

Glycine receptors have also been shown to exist in adult forebrains mainly extrasynaptically and also taurine and β-alanine act as possible endogenous agonists as well as GABA, and glycine itself.

Glycine and D-serine function as co-transmitter for NMDA receptors. Papouin., *et al.* however, have shown that D-serine works primary on the synaptic NMDA receptor, while glycine works on extrasynaptic NMDA receptors [33].

The cerebrospinal fluid of the developing and mature brain is flooded with putative endogenous modulators including GABA, glycine, taurine, β-alanine, together with other transmitters released synaptically or non synaptically by neurons or glia and other non-neural cells and absorbed or catalysed by them and regulating function of CNS.

Extrasynaptic transmission and neurological disorders

Abnormality of E/I balance in CNS, which is also expressed as GABA/glutamate balance thought to be governed by tonic inhibitory effect through GABAA receptors and excitatory effect through NMDA or other glutamate receptors, is thought to relate not only autism spectrum disorders but also various kinds of neural disorders including epilepsy, schizophrenia and Alzheimer diseases. Cytotoxic activity of extrasynaptic NMDA receptors is also related to many types of neural disorders. These two mechanisms sometimes seem to be related in complex ways [34]. In the treatment of neurological diseases, therefore, it is necessary to develop therapy aimed at the Extrasynaptic transmissions have been shown to system [1]. In fact, many psychotic drugs are known to act on extrasynaptic receptors [1,35].

Conclusion

Looking at the current fully evolved structures, the CNS and its neural network consisting of cell bodies, dendrites, axons, and synapses exist as main circuitry, and the extrasynaptic signalling appears to be an auxiliary mechanism. However, if the evolution is the result of random trial and error in the first place, it is rather strange that there is a clear distinction between those systems in the process of using the convenient parts. In addition, the relationship between the nervous system and other signaling systems, such as the endocrine and immune systems, is similar, and sometimes the boundaries are ambiguous, as in the case of oxytocin vasopressin secretion in hypothalamus. It is expected that the concept of a biological information transmission system including all of these will become important.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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