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Chapter

Synaptic Transmission and Amino Acid Neurotransmitters

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Abstract

Amino acids are the most abundant neurotransmitters in the brain. Neurotransmitters are synthesized and stored in presynaptic terminals, released from terminals upon stimulation with specific receptors on the postsynaptic cells. Chemical and electrical synapses are specialized biological structures found in the nervous system; they connect neurons together and transmit signals across the neurons. The process of synaptic transmission generates or inhibits electrical impulses in a network of neurons for the processing of information. Glutamate is the primary excitatory neurotransmitter in the brain, while GABA is the principal inhibitory neurotransmitter. The balance of glutamatergic and GABAergic tone is crucial to normal neurologic function. Through synaptic transmission, this information is communicated from the presynaptic cell to the postsynaptic cell. Amino acid neurotransmitters primarily glutamic acid, GABA, aspartic acid, and glycine are single amino acid residues released from presynaptic nerve terminals in response to an action potential and cross the synaptic cleft to bind with specific receptor on the postsynaptic membrane. The integral role of amino acid neurotransmitters is important on the normal functioning of the brain. The presynaptic and postsynaptic events in chemical synapses are subject to use dependent and highly regulated as per the changes in synaptic neurotransmitter release and function.

Keywords: synapse, neurotransmitter, receptor, glutamate, GABA, glycine, aspartate

1. Introduction

The nervous system is composed of billions of specialized cells called neurons. Neurons are the cells of chemical communication in the brain. In its most basic form, a neuron has two ends (although either can have multiple branches): an axon and a dendrite (**Figure 1**). Efficient communication between neuronal cells is a crucial process for the normal functioning of the central and peripheral nervous system. Neurotransmitters are chemical substances that act as the mediator for the transmission of nerve impulses from one neuron to another neuron through synapses. Neurotransmitters are stored in the axon (or presynaptic neuron) in little packages called synaptic vesicles. The release of neurotransmitter is triggered by the arrival of nerve impulse (or action potential). Synapses are specialized junctions through which cells of the nervous system signal to one another and to non-neuronal cells such as muscles or glands. The process by which the information is communicated through synapse is called synaptic transmission [1, 2].

The neurotransmitters are stored in the vesicles within the presynaptic nerve terminal at the synaptic membrane of one nerve cell and released into the synaptic

cleft in response to nerve impulses [2]. The secreted neurotransmitters can then act on receptors on the membrane of the postsynaptic neuron through a gap called synaptic gap (0.02 micron). The number of synaptic contacts of an average neuron is approximately 10,000. Thus, there are 3–5 × 10^{15} synapses in the human brain. There are two types of synapses, electrical and chemical synapses, but chemical synapses (**Figure 2**) far outnumber electrical ones. Electric synapses are gap junction. A gap junction is a junction between neurons that allows different molecules and ions to pass freely between cells. The junction connects the cytoplasm of cells. A gap junction is composed of connexons (each connexon is composed of six connexin proteins) which connect across the intercellular space. Neurons connected by gap junctions sometimes act as though they were equivalent to one large neuron with many output pathways, all of which fire synchronously.

Synapses are made on all regions of a receiving nerve cell and can be classified on the basis where they are located. On spiny dendrites of a nerve cell, each spine is the target of an axon terminal and comprises the postsynaptic component of a single synapse. Synapses between axons and dendrites are called axodendritic. Particularly powerful synapses are made between axons of one neuron and cell body of another postsynaptic cell. These are called axosomatic synapses. Synapses between axon terminals and axons of postsynaptic neurons are said to be axo-axonal.

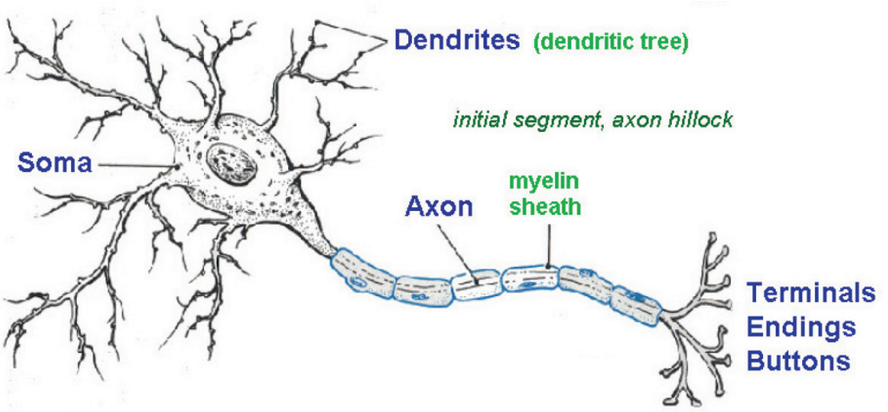

Figure 1.
Structure of neuron.

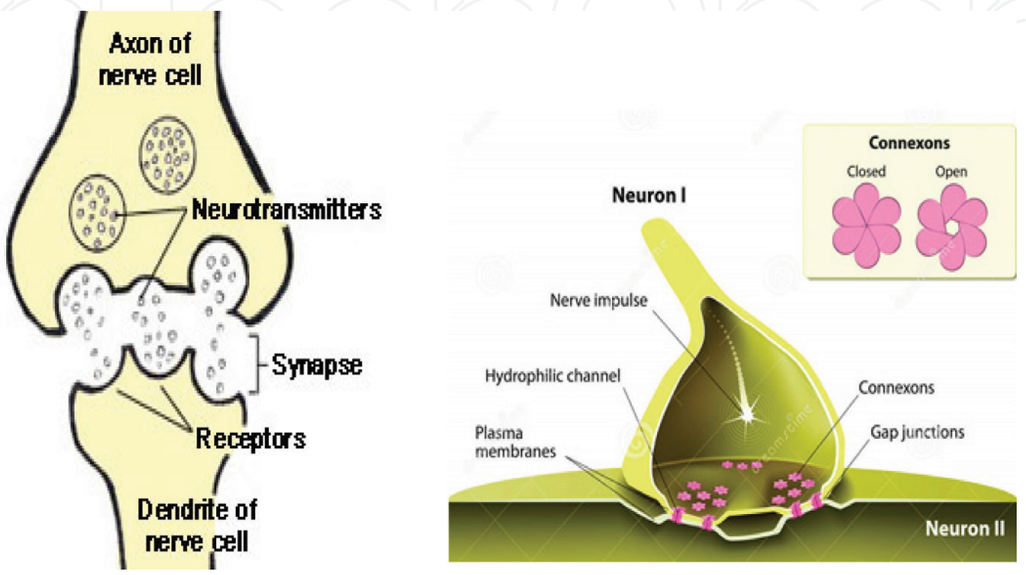

Figure 2.
Structure of chemical and electrical synapse.

Substances that act as neurotransmitters can be categorized into different groups. The three major categories of substances that act as neurotransmitters are:

1. Amino acids: The neurotransmitters of this group are involved in fast synaptic transmission and are inhibitory and excitatory in action (primarily glutamic acid, GABA, aspartic acid, and glycine).

2. Amines: Amines are the modified amino acids such as biogenic amines, e.g., catecholamines. The neurotransmitters of this group involve in slow synaptic transmission and are inhibitory and excitatory in action (noradrenaline, adrenaline, dopamine, serotonin, and histamine).

3. Others: The one which do not fit in any of these categories (acetyl choline and nitric oxide). Amino acids are among the most abundant of all neurotransmitters present within the central nervous system (CNS).

Several amino acids have been implicated as neurotransmitters in the CNS, including GABA, glutamic acid, glycine, and aspartic acid [3]. Some (like glutamate) are excitatory, whereas others (like GABA) are primarily inhibitory. Aspartate is closely related to glutamate, and the two amino acids are often are found together at axon terminals. Neurons synthesize glutamate and aspartate and are independent of dietary supply.

1.1 Function of amino acid neurotransmitter

The amino acid neurotransmitters are common neurotransmitters in the central nervous system. Glycine, glutamate, and GABA are classed under amino acid neurotransmitter. The two amino acids functioning as excitatory neurotransmitter are glutamate and aspartate. GABA acts as a brake to the excitatory neurotransmitters, and thus when it is abnormally low, this can lead to anxiety, and glutamate usually ensures homeostasis with the effects of GABA [4]. Several related amino acids, like homocysteic acid and N-acetylaspartylglutamate, may also serve a neurotransmitter function. Neurotransmitters can be classified as either excitatory or inhibitory. Excitatory neurotransmitters function to activate the receptors on the postsynaptic membrane and enhance the effects of action potential, while inhibitory neurotransmitter functions in a reverse mechanism. If the electrical impulses transmitted inward toward the cell body are large enough, they will generate an action potential.

The action potentials are caused by an exchange of ions across the neuron membrane; a stimulus first causes sodium channels to open, because there are many more sodium ions on the outside, and the inside of the neuron is negative relative to the outside; sodium ions rush into the neuron. Since sodium has a positive charge, the neuron becomes more positive and becomes depolarized. It takes longer for potassium channels to open; when they do open, potassium rushes out of the cell, reversing the depolarization. Also at about this time, sodium channels start to close; this causes the action potential to go back toward −70 mv (a repolarization). The action potential actually goes past (overshoots) −70 mv (a hyperpolarization) because the potassium channels stay open a bit too long. Gradually, the ion concentrations go back to resting levels, and the cell returns to −70 mv.

The action potential is produced by an influx of calcium ions through voltage-dependent calcium-selective ion channels. Calcium ions then trigger a biochemical cascade which results in neurotransmitter vesicles fusing with the presynaptic membrane and releasing their contents to the synaptic cleft. Receptors on the opposite side of the synaptic gap bind neurotransmitter molecules and respond

by opening nearby ion channels in the postsynaptic cell membrane, causing ions to rush in or out and changing the local transmembrane potential of the cell. The resulting change in voltage is called a postsynaptic potential. The result is excitatory, in the case of depolarizing currents, or inhibitory in the case of hyperpolarizing currents resulting in EPSP or IPSP, respectively (**Figure 3**).

Whether a synapse is excitatory or inhibitory depends on what type(s) of ion channel conduct the postsynaptic current, which in turn is a function of the type of receptors and neurotransmitter employed at the synapse. Neurotransmitters may have excitatory effects if they drive a cell's membrane to the threshold of an action potential (**Figure 4**).

The resting potential of a neuron tells about what happens when a neuron is at rest. An action potential occurs when a neuron sends information down an axon, away from the cell body. The action potential is an explosion of electrical activity that is created by a depolarizing current. This means that a stimulus causes the resting potential to move toward 0 mv.

1. When the depolarization near the axon hillock reaches about −55 mv as a result of summation of EPSPs, a neuron will fire an action potential. This is the threshold. If the neuron does not reach this critical threshold level, then no action potential will fire.

2. Also, when the threshold level is reached, an action potential of a fixed sized will always fire for any given neuron; the size of the action potential is always the same.

There are no big or small action potentials in one nerve cell. All action potentials are the same in size in a particular neuron type (it can differ between different types of neurons). Therefore, either the neuron does not reach the threshold or a full action potential is fired—this is the "all or none" principle.

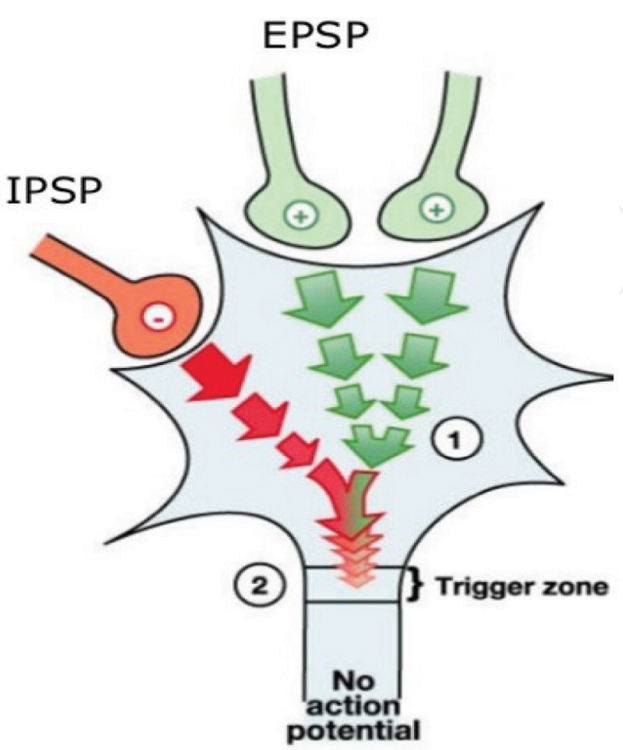

Figure 3.
EPSP and IPSP on a neuron.

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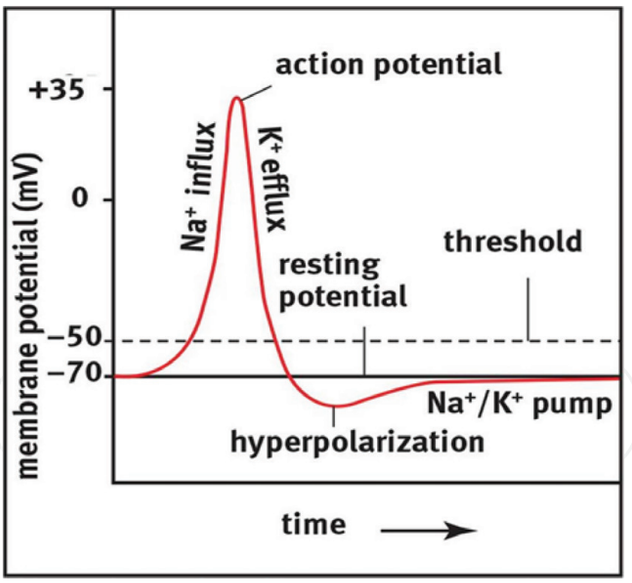

Figure 4.
Action potential.

A neuron encodes the intensity of a stimulus in the frequency of firing and not in the size of a single impulse. Neurotransmitters may have inhibitory effects if they help to drive the membrane away from threshold. An excitatory postsynaptic potential (EPSP) is a summation of signals that brings the membrane closer to the threshold (depolarizing effect). An inhibitory postsynaptic potential (IPSP) drives the membrane away from threshold by a hyperpolarizing effect.

1.1.1 Excitatory neurotransmitters

An excitatory postsynaptic potential (EPSP) is a temporary increase in postsynaptic membrane potential within dendrites or cell bodies caused by the flow of sodium ions into the postsynaptic cell. EPSPs are additive. Larger EPSPs result in greater membrane depolarization and thus increase the likelihood that the postsynaptic cell reaches the threshold for firing an action potential. When an active presynaptic cell releases neurotransmitters into the synapse, some of them bind to receptors on the postsynaptic cell. Many of these receptors contain an ion channel capable of passing positively charged ions either into or out of the cell. At excitatory synapses, the ion channel typically allows sodium into the cell, generating an excitatory postsynaptic current.

1.1.2 Inhibitory neurotransmitters

GABA and glycine are inhibitory, both instead of depolarizing the postsynaptic membrane and producing an EPSP; they hyperpolarize the postsynaptic membrane and produce IPSP. IPSP is the change in membrane voltage of a postsynaptic neuron which results from synaptic activation of inhibitory neurotransmitter receptors. The most common inhibitory neurotransmitters in the nervous system are γ-aminobutyric acid (GABA) and glycine. At a typical inhibitory synapse, the postsynaptic neural membrane permeability increases for K^+ ions and Cl^- ions but not for Na^+ ions.

This generally causes an influx of chloride ions and efflux of K^+ ions, thereby bringing the membrane potential closer to the equilibrium potential of these ions.

2. Amino acid neurotransmitters

Amino acid transmitters provide the majority of excitatory and inhibitory neurotransmission in the nervous system. Amino acids used for synaptic transmission are compartmentalized (e.g., glutamate, compartmentalized from metabolic glutamate used for protein synthesis by packaging the transmitter into synaptic vesicles for subsequent Ca^{2+}-dependent release). Amino acid neurotransmitters are all products of intermediary metabolism with the exception of GABA. Unlike all the other amino acid neurotransmitters, GABA is not used in protein synthesis and is produced by an enzyme (glutamic acid decarboxylase; GAD) uniquely located in neurons. Antibodies to GAD can be used to identify neurons that release GABA.

2.1 Glutamate

Glutamate is used at the great majority of fast excitatory synapses in the brain and spinal cord. Glutamatergic neurons are particularly prominent in the cerebral cortex. They project to a variety of subcortical structures like the hippocampus, the basolateral complex of the amygdala, the substantia nigra, the nucleus accumbens, the superior colliculus, the caudate nucleus (nucleus ruber), and the pons. At glutamatergic synapses, NMDA receptors (NMDARs) are localized with other ionotropic glutamate receptors [AMPA receptors (AMPARs) and kainate receptors] and with metabotropic glutamate receptors. Glutamate receptors are necessary for neuronal development, synaptic plasticity, excitotoxicity, pain perception, and learning and memory [5]. Among these EPSP-producing glutamate receptors, which could occur as homomeric or heteromeric structures, are classified according to the binding of the most common agonist [6].

Four subtypes can be distinguished, out of which three are ionotropic receptors and one metabotropic receptor, activated by quisqualate. These are named according to the molecules (other than glutamate) that they bind and include:

1. NMDA receptors (named for N-methyl-D-aspartate)

2. AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate)

3. Kainate receptors

4. Receptors which are activated by quisqualate

2.1.1 NMDA receptors

NMDA receptor is very important for controlling developmental synaptic plasticity and learning and memory function. NMDARs have critical roles in excitatory synaptic transmission, plasticity, and excitotoxicity in the CNS (**Figure 5**). The NR1 subunit is evenly expressed in most of the brain, but the NR2 subunit (NR2A, NR2B, NR2C, and NR2D) shows distinct regional distributions [6, 7]. NMDA receptors show three specific properties by which they differ from other types of ionotropic receptors:

a. NMDA receptor ion channel is subjected to voltage-dependent block by the extracellular Mg^{2+} ion.

b. They display a high permeability to Ca^{2+} ions. Ca^{2+} influx through NMDA receptor channel leads to a cascade of intracellular events triggering long-term potentiation (LTP) and long-term depression (LTD) of synaptic currents.

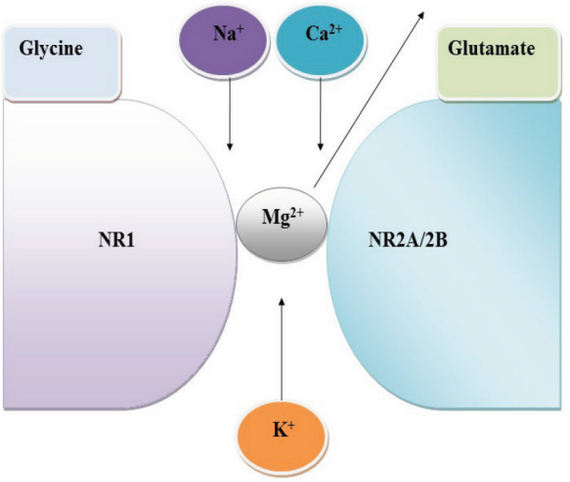

Figure 5.
NMDA receptor.

c. The response of NMDA receptor to neurotransmitter like glutamate and glycine under physiological conditions is modified by certain extracellular molecules like H^+, Zn^{2+}, and polyamines. Most of the NMDA receptors function only in heteromeric assemblies, composed of two NR1 and two NR2 subunits.

Glutamate binds to the S1 and S2 regions of NR2 subunit, whereas glycine binds to the S1 and S2 regions of NR1 subunit. Individual NR1 or NR2 subunits contain an extracellular N terminus which forms S1, an intracellular C terminus, and an extracellular loop between M3 and M4 that constitutes S2. The channel lining domain is formed by a reentrant pore loop called as M2 loop that enters the channel from the cytoplasmic side and forms a narrow constriction at that channel. The critical asparagine residue located within M2 loop determines the selectivity of NMDAR channel for Mg^{2+} block and Ca^{2+} permeability.

The function of NMDA receptors is totally dependent upon AMPA receptors. In the absence of AMPA, NMDA is initially expressed, and it forms the silent synapse. The NMDA receptors are not activated unless the postsynaptic region is depolarized by AMPA receptors.

AMPA receptors are ionotropic and belong to the group of non-NMDA receptors and associated with a cation-selective ion channel which is permeable for monovalent cations, like Na^+ and K^+. Under certain combinatorial conditions of the receptor subunits, it also becomes permeable to Ca^{2+}.

Kainate receptors can be activated by kainite and glutamate. Like AMPA receptors, the kainite receptors are associated with an ionic channel which is permeable for the monovalent cations Na^+ K^+ and for Ca^{2+}. These receptors are mainly involved in modulating the release of excitatory amino acids and additional neurotransmitters or neuromodulators.

The metabotropic receptors are activated by glutamate and quisqualate and resistant to activation by NMDA, AMPA, or kainate.

2.2 GABA

GABA is the most ubiquitous inhibitory neurotransmitter in the brain. GABA was discovered in 1883, and its inhibitory function was described in the late 1950s by Bazemore et al. [8]. It was the first amino acid to be established as a neurotransmitter in vertebrate and invertebrate nervous systems. GABA is synthesized in nervous tissue exclusively from glutamate by the alpha decarboxylation of glutamic

acid in the presence of glutamic acid decarboxylase (GAD). The apparent prominent role of GAD in modulation of GABA levels becomes obvious under pathological conditions, where GAD concentration can differ significantly from normal levels.

Striatum contained nearly 95% of the cells which are GABAergic. GABA is also suspected to operate as an inhibitory neurotransmitter in the cerebral cortex, lateral vestibular nucleus, and spinal cord.

2.2.1 GABA receptors

GABA exerts its effects via ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors. $GABA_A$ receptors show a ubiquitous distribution throughout the CNS and have been identified on both neuron and glia. GABA can act on both rapid and slow inhibitory receptors (the $GABA_A$ and $GABA_B$), respectively. $GABA_A$ receptors are chloride channels that in response to GABA binding increases chloride influx into the neuron. The agonist of these receptors includes GABA and muscimol. The $GABA_B$ receptors are potassium channels that when activated by GABA leads to potassium efflux from the cell. $GABA_A$ receptors are ionotropic receptors leading to increased Cl^- ion conductance, whereas $GABA_B$ receptors are metabotropic receptors which are coupled to G proteins and thereby indirectly alter membrane ion permeability and neuronal excitability [4].

2.3 Glycine

Glycine is the simplest of amino acids, consisting of an amino group and a carboxyl (acidic) group attached to a carbon atom. In mammals, glycine belongs to the nonessential amino acids [9]. Until the early 1960s, glycine was of minor importance in synaptic transmission because of its simple structure and its ubiquitous distribution as a member of protein and nucleotide metabolism. Glycine's function is a potent neurotransmitter in the spinal cord and brain. Glycine is a constituent of glutathione, an antioxidant tripeptide found in high concentrations in intestinal epithelial cells. The availability of glycine has the potential to control the cellular levels of glutathione in enterocytes. This amino acid functions as an excitatory transmitter during embryonic development and is an essential coagonist at glutamatergic synapses containing the NMDA subtype of glutamate receptors. Hydroxymethyl transferase converts the amino acid serine to glycine. More recently, glycine has been found to play a role in the functional modulation of NMDA receptors.

2.3.1 Glycine receptor

Glycine receptors are ligand-gated ion channels that increase Cl^- influx. Glycine molecules may be taken back into the presynaptic cell by two high-affinity glycine transporters (Glyt-1 and Glyt-2). Glyt-1 is found primarily in glial cells, whereas Glty-2 is found primarily in neuronal cells. The transport of glycine via Glyt-1 is coupled to the movement of Na^+ and Cl^-, with a Na^+:Cl^-:glycine stoichiometry of 2:1:1.

The glycine receptor GlyR belongs to the superfamily of ligand-gated ion channels, like $GABA_A$, and is primarily found in the ventral spinal cord. Strychnine is a glycine antagonist which can bind to the glycine receptor without opening the chloride ion channel (i.e., it inhibits inhibition). GlyR is a strychnine-sensitive glycoprotein which is composed of five subunits. The receptor has a pentameric structure with three ligand-binding α subunits and two β subunits forming an ion channel. This heterogenicity is responsible for the distinct pharmaceutical and

functional properties displayed by the various receptor configurations that are differentially expressed and assembled during development [10].

The glycine receptor is presently considered to form a complex consisting of a glycine recognition site and an associated chloride channel. Hyperekplexia, or startle disease, is a rare neurological disorder characterized by an exaggerated response to unexpected stimuli. The response is typically accompanied by a transient but complete muscular rigidity (stiff baby syndrome).

2.4 Aspartate

Glutamate and aspartate are nonessential amino acids that do not cross the blood-brain barrier and, therefore, are synthesized from glucose and a variety of other precursors. The synthetic and metabolic enzymes for glutamate and aspartate have been localized to the two main compartments of the brain, neurons and glial cells. Aspartate is the most abundant excitatory neurotransmitter in the CNS. Like glycine, aspartate is primarily localized to the ventral spinal cord. Like glycine, aspartate opens an ion channel and is inactivated by reabsorption into the presynaptic membrane. Unlike glycine, however, aspartate is an excitatory neurotransmitter, which increases the likelihood of depolarization in the postsynaptic membrane [9, 10]. Aspartate is a highly selective agonist for NMDAR-type glutamate receptors and does not activate AMPA-type glutamate receptors. Hence, synapses only releasing aspartate should therefore generate only NMDAR currents despite a full postsynaptic complement of AMPARs [11].

Aspartate and glycine form an excitatory/inhibitory pair in the ventral spinal cord comparable to the excitatory/inhibitory pair formed by glutamate and GABA in the brain. Interestingly, the two excitatory amino acids, glutamic acid and aspartic acid, are the two acidic amino acids found in proteins, insofar as both have two carboxyl groups rather than one. Thus, variation in the vesicular content of glutamate and aspartate might have a profound effect on the relative contribution of NMDARs and AMPARs to synaptic transmission [12, 13].

3. Conclusion

Neurotransmitters are the brain chemicals that communicate information throughout our brain and body. They relay signals between neurons. Amino acid neurotransmitters can be subdivided into the excitatory amino acids aspartate and glutamate and the inhibitory amino acids GABA and glycine. Common inhibitory neurotransmitters such as GABA and glycine calm the brain and help create balance, whereas excitatory neurotransmitters such as glutamate and aspartate stimulate the brain.

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Conflict of interest

The authors declare that they have no conflict of interest.

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