Chapter 1

Introductory Chapter: GABA/Glutamate Balance: A Key for Normal Brain Functioning

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1. Introduction

The basis of information transfer in the mammalian central nervous system (CNS) consists of excitation and inhibition of neuronal networks. The messengers responsible for propagating these excitatory and inhibitory actions are amino acid neurotransmitters [1]. The principal excitatory neurotransmitter is glutamate, while the principle inhibitory neurotransmitter is gamma-aminobutyric acid (GABA). Coordination between these two principal neurotransmitters ensures adequate rhythmic activity, which may involve either a single neuron or multiple neuronal groups, thus altering synaptic plasticity and ensuring a normal functioning of CNS [2]. As this spatiotemporal framework of different patterns in neural oscillations is essential for information processing throughout the brain [3], the deviations in normal activity of either system or their interactions are associated with a number of neurological and psychiatric diseases [4].

The GABA/glutamate functional balance could be achieved by homeostatic control of presynaptic elements such as glutamate and GABA release, which could be the result of changes in their metabolism (synthesis or degradation involving various enzymes), compartmentation, and recycling (involving plasma transporters) and in the amounts of transmitters available for release from synaptic vesicles (involving vesicular transporters). However, it is generally considered that homeostatic plasticity mechanisms in the brain are mediated primarily by regulation of expression and function of glutamate and GABA receptors [5].

2. GABA and its receptors

Every third chemical synapse in the brain uses neurotransmitter GABA as an integral part of the neurotransmission process. GABA mediates its effects via two types of receptors: ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors [6]. Although a third type of GABA receptor with pharmacological specificities has been identified, the term $GABA_C$ has not received broad consensus among experts. Additionally, the International Union of Basic and Clinical Pharmacology (IUPHAR) has classified $GABA_C$ as a type of $GABA_A$ receptor [7].

$GABA_A$ receptors generally contain chloride ion channels but can, in varying degrees, also contain calcium, sodium, and potassium channels. $GABA_A$ receptors mediate the majority of GABA inhibitory actions in the CNS [4]. They are pentameric transmembrane receptors made up of 5 subunit proteins that form an ion channel selectively permeable to chloride anions. Although mainly localized on postsynaptic membranes, they can also be found extrasynaptically, especially $GABA_A$ receptors containing α4, α5, or α6 subunits [8]. Unexpectedly, $GABA_A$ receptors have also been found on glial cells, potentially providing adaptational support for adjacent neurons [9]. Activation of $GABA_A$ receptors leads to a change in the conformational state of associated ion channels, resulting in increased permeability to chloride ions. GABAergic mechanisms are also involved in metabolic processes [10], and a negative correlation between the intensity of GABAergic neurotransmission and metabolic processes in cerebral tissue has been established. So far, 19 subunits of $GABA_A$ receptors have been cloned and classified into several structurally related subfamilies (α 1–6, β 1–3, γ 1–3, δ, ε, θ, π, ϱ 1–3). The most frequently found $GABA_A$ receptor composition is an aggregate composed of two α, two β, and one γ subunit [4]. Receptors that, in addition to two α and two β subunits, contain some other non-γ subunit are rare. Receptors composed only of α and β isoforms also exist. The subunit composition determines the functional and pharmacological properties of $GABA_A$ receptors. For example, α1 $GABA_A$ receptors mediate sedative and anticonvulsant actions, whereas the α2 subunit is responsible for anxiolytic action of benzodiazepines. Zolpidem, a commonly prescribed sedative for sleep initiation, has a high binding affinity for $GABA_A$ receptors containing the α1 subunit [11].

GABA action through $GABA_A$ receptors results in chloride channel opening and increased postsynaptic membrane permeability. In addition to the well-determined benzodiazepine binding site, at least 13 different and structurally specific sites on the $GABA_A$ receptors have been identified: (1) GABA and other agonist-binding sites, as well as competitive antagonists; (2) picrotoxin site near ion channel; (3) barbiturates binding site; (4) neuroactive steroids binding site; (5) ethanol binding site; (6) inhalation anesthetics stereoselective binding sites; (7) furosemide diuretic binding site; (8) Zn^{2+} ion binding site; (9) other divalent cation binding sites; (10) La^{3+} ions site; (11) sites for phosphorylation of specific protein kinases; (12) phospholipid-binding sites; and (13) sites involved in interaction of $GABA_A$ receptor and microtubules, which promote receptor grouping on postsynaptic membranes [12]. Modulators of $GABA_A$ receptor complex interact with these binding sites in three possible ways: positive allosteric modulators that potentiate chloride ion flux (agonists), negative modulators that reduce GABA-induced chloride ion flux (inverse agonists), and neutral allosteric modulators that competitively block the effects of these two types of agonists-antagonists.

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On the other hand, $GABA_B$ metabotropic receptors, characterized by stereoselective ligand (−) baclofen, belong to the seven transmembrane G-protein-coupled receptor superfamily. They are pre- and postsynaptic G-protein-coupled receptors that negatively modulate adenylyl cyclase and inositol triphosphate synthesis. Heterodimeric structure as a result of GABAB1 and GABAB2 subunit assembly is necessary for appropriate $GABA_B$ receptor function. The extracellular domain of the GABAB1 subunit contains GABA-binding site, whereas GABAB2 subunit is important for the interaction with the G-proteins. $GABA_B$ receptor activation produces a cascade of signals that result in activation and/or inhibition of voltage-dependent calcium channels. $GABA_B$ receptor is located both centrally and peripherally, particularly in the thalamus, brain stem nuclei, and spinal cord. Depending on the localization of $GABA_B$ receptors, GABA-mediated inhibitory influences can be potentiated (postsynaptic receptors, presynaptic heteroreceptors on glutamatergic endings) or reduced (autoreceptors) [13, 14]. GABAB receptor function affects behavior, learning, and memory, and therefore their pharmacological targeting may be beneficial in various neuropsychiatric disorders [15, 16].

3. Glutamate and its receptors

Glutamate, the most abundant neurotransmitter in vertebrates and precursor of GABA, is present in over 90% of all synaptic connections in the human brain and is essential for a wide variety of functions [17]. Over 20 types of mammalian glutamate receptors exist, generally classified into two main categories: voltage-sensitive (ionotropic) and ligand-sensitive (metabotropic) receptors. Ionotropic receptor channels are formed from various protein subunits assembled in heterotetrameric or homotetrameric receptors. The three types of ionotropic receptors are N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainic acid receptors. The discovery of these agonists, after which the receptors were originally named, led to the detection of other receptor agonists and antagonists [18].

The binding of glutamate to NMDA receptors (NMDARs) results in the opening of a nonselective cation channel. The opening and closing of the channel are primarily gated by ligand binding but are also voltage-dependent. Extracellular magnesium and zinc ions can bind to specific sites on the receptor, blocking the passage of other cations through the open ion channel. However, depolarization of the neuronal cell dislodges and repels these ions from the pore, therefore allowing a voltage-dependent influx of sodium and calcium ions and efflux of potassium ions [19]. The NMDA receptor is primarily a ligand-gated channel, but it does display weaker voltage-dependent modulation of the ligand-dependent gating. NMDA requires co-activation by two ligands: glutamate and either D-serine or glycine [20]. Furthermore, NMDA receptors are divided into subtypes, depending on their intracellular protein structure, NR1, NR2, and NR3. NR1 consists of eight different subunits originating from a single gene via alternative splicing. NR2 has four subunits (A–D), and NR3 has two subunits (A and B). NMDA receptors are highly expressed on both neurons and astrocytes [21]. NMDA signaling is crucial for learning, memory, recovery from injury, and brain plasticity. It is especially important for proper functioning of the hippocampus [22]. In pathological circumstances, overactivation of NMDA receptors can lead to excitotoxicity, involved in some neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease [23–25].

AMPA receptors (AMPAR) are composed of four types of subunits, designated as GluA1, GluA2, GluA3, and GluA4 [26]. These receptors are heterotetrameric, containing GluA2 and either GluA1, GluA3, or GluA4 subunits in a "dimer of dimers" structure [27, 28]. Each AMPAR consists of four subunits which make up four binding sites to which an agonist (such as glutamate) can bind. The channel opens when two binding sites are simultaneously occupied, and the current increases as more binding sites become occupied [29]. Once opened, the channel may undergo rapid desensitization and current termination. Since AMPARs open and close quickly (1 ms), they are responsible for fast excitatory synaptic transmission in the CNS [30]. The GluA2 subunit regulates whether the AMPAR is permeable to calcium and other cations, such as sodium and potassium. If receptor does not contain a GluA2, the AMPAR will be permeable to calcium, sodium, and potassium. Both NMDA and AMPA ion channels are important for plasticity and synaptic transmission at many postsynaptic membranes.

Kainate receptors (KAR) are heteromeric receptors assembled from four subunits, formerly referred to as GluR5, GluR6, GluR7, KA1, and KA2 but now named GluK1, GluK2, GluK3, GluK4, and GluK5, and grouped into low affinity (GluK1–3) and high affinity (GluK4–5) receptors. Each subunit has a large extracellular N-terminal domain, four helical transmembrane domains (M1–M4), and an intracellular C-terminal domain. GluK1–3 subunits can form both homomeric and heteromeric receptors, but GluK4 and GluK5 subunits can form only heteromeric functional ion channels together with GluK1–3 subunits. Despite their ion channel structure, KAR can also activate metabotropic signaling through noncanonical G-protein-coupled cascade. They are widely distributed in the brain and can be localized at pre-, post-, and/or extrasynaptic sites. Although KAR are less studied than AMPAR or NMDAR, it is not known that they are multifunctional neuronal modulators which play significant roles in health and disease [31].

Metabotropic glutamate receptors (mGluR) have a G-protein-linked receptor structure consisting of seven transmembrane domains with an extracellular N-terminal and an intracellular COOH terminal. When glutamate binds to a metabotropic receptor, it activates a postsynaptic intracellular G-protein, which eventually results in the opening of a membrane channel for signal transmission. Furthermore, G protein activation also triggers functional changes in the cytoplasm, resulting in gene expression and protein synthesis. For this reason, mGluR is generally considered slower acting channels than the ionotropic glutamate receptors. To date, three groups of mGluR exist. Group I receptors are coupled with phospholipase C, producing diacylglycerol and inositol triphosphate as second messengers. They are mainly expressed on the postsynaptic membrane. Group I receptors are involved in learning and memory, addiction, motor regulation, and Fragile X syndrome [32]. Groups II and III are negatively coupled to adenylyl cyclase. Impaired functioning of group II metabotropic receptors has been linked to anxiety, schizophrenia, and Alzheimer's disease. Group III metabotropic receptors also inhibit neurotransmitter release but are positioned presynaptically. They are found within the hippocampus and hypothalamus and may play a role in Parkinson's disease and anxiety disorders [33].

4. Conclusion and clinical implications

The adequate coordination of GABA and glutamate is essential to the normal functioning for the most complex brain processes. Decreased or increased GABA activity is associated with a

number of neurological and psychiatric diseases. The GABAergic synapse is the site of action of several different classes of drugs that modulate inhibitory neurotransmission and are used in the pharmacotherapy of anxiety and sleep disorders, epilepsy, alcohol withdrawal, and induction and maintenance of anesthesia [34]. Moreover, glutamate dysfunction is also correlated with a wide range of nervous system disorders, such as Alzheimer's disease, and neuropsychiatric disorders, including schizophrenia, pain disorders, drug addiction, and traumatic brain and spinal cord injuries [35]. Given the importance of equilibrium of these two systems for neuronal excitability, synaptic plasticity, and cognitive functions such as learning and memory, as well as its involvement in the mood, feeding behavior, reproductive functions, pain sensitivity, aging, etc. [36], it is not surprising that the development of current and prospective pharmaceuticals, including anxiolytics, antidepressants, antipsychotics, antiepileptics, antidementia, and many other drugs, relies increasingly on GABA/glutamate balance.

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