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Chapter

Introductory Chapter: The Chemical Basis of Neural Function and Dysfunction

Thomas Heinbockel and Antonei B. Csoka

1. Introduction

What is neurochemistry? As a field of study, neurochemistry is concerned with the types, structures and functions of the chemical components found in the nervous system [1]. These components in turn regulate the physiology of the nervous system [2–4]. Neurochemistry is mainly concerned with the chemicals that are specifically found in the nervous system such as small organic molecules, neurotransmitters and neuropeptides. Neurological diseases are often a reflection of changes in the body's neurochemistry, e.g., in Alzheimer's disease or Parkinson's disease. Medicine uses neurochemicals to alter brain function and treat disease. Neurochemists study how the components of the nervous system are at work during processes such as neural plasticity, neural development, learning and memory formation and how these components undergo changes during disease processes, neural dysfunction, and aging. This chapter will introduce the chemical components of the nervous system and briefly discuss how external and internal factors impact and modify these components.

2. Building blocks of the nervous system

The nervous system comprises a vast array of cells that vary in form and function and how they interact with other cells. The two principal types of cells are nerve cells or neurons and glial cells. Both types have many subtypes that are named based either on their shape or function. Neurons can be broadly classified as unipolar, bipolar, multipolar or pseudounipolar based on their arrangement and presence of dendrites and axons, or they are classified as sensory, motor or interneurons based on their function in neural networks. Dendrites are considered as the recipient portion of a nerve cell while axons carry information to other parts of the nervous system. However, this distinction can be blurred in neural circuits where both axons and dendrites can serve in either function. Axons reach a length of 1.5 m in adult humans and are even longer in larger animals such as giraffes. While axons serve as long-distance communication devices for information through the propagation of action potentials, axons also transport physical material toward the axonal terminal and from the terminal to the cell body. Protein synthesis takes place in the cell body where genetic information is located. Therefore, all proteins and also organelles such as mitochondria that are needed in the axon terminal have to be shipped down the axon with the help of motor proteins. Two motor proteins, kinesin and dynein, move vesicles or organelles along microtubules in the axon.

Kinesin moves vesicles toward the terminal or away from the center of the neuron (anterograde axonal transport) while dynein moves in the opposite direction, namely from the terminal toward the cell body (retrograde axonal transport).

Glial cells also come in different flavors. Glial cells are increasingly recognized for their physiological functions in the nervous system and have been named "the unsung heroes of the brain" [5]. Certain glial cell types are found only in the peripheral nervous system such as satellite cells or myelin-forming Schwann cells, while others are housed in the central nervous system (brain and spinal cord) such as astrocytes (fibrous and protoplasmic), microglia and myelin-forming oligodendrocytes. Despite these commonly accepted classifications, it should be clear that nerve cells are so varied in their morphology that it has been virtually impossible to adequately classify them based on shape, ultrastructure, neurotransmitter profile, physiology or location. Furthermore, neurons with similar form and function have been described in distant animal taxa that do not share recent phylogenetic relations.

Nerve cells are equipped with cellular machinery that is present in most other cell types such as nucleus, Golgi apparatus, mitochondria, smooth and rough endoplasmic reticulum. Histological staining of nerve cells with dyes such as toluidine blue or cresyl violet (Nissl staining, nucleic acid stain) reveals particularly intense labeling of the nucleolus and Nissl substance in the cytoplasm [6]. Nissl substance refers to free ribosomes in the cytoplasm and bound ribosomes on the ER. This heavy staining pattern is a reflection of the active metabolism and continuous production of peptides and proteins in nerve cells and identifies nerve cells among the most active cells in the body.

3. Excitable cell membranes and channelopathies

Nerve cells and glial cells are compartmentalized by membranes that are built by lipids and proteins. These lipids and proteins are key elements for the unique functional role each neuron plays in the neural circuit and for the intracellular activities that occur in axons and dendrites distant from the cell nucleus. During development, axonal guidance and remodeling of dendritic spines are shaped in response to signal input at local membrane compartments which is communicated to the cell interior through specific receptors and channels. The inside and outside of the cellular membranes are different from each other, such that an asymmetric distribution of lipids and proteins between cytoplasmic and exoplasmic leaflets allows for an unequal division of labor [1]. Lipids are critically relevant for the structure and function of the nervous system. Membrane lipids are the main component of the myelin that ensheathes axons both in the central and peripheral nervous system. Furthermore, at the connections between nerve cells, the synapses, membranes have unique lipid compositions. The synapse is equipped with a synaptic machinery of vesicles and proteins that contribute to the specialized properties of these membrane compartments and to the plastic changes in synaptic transmission from pre- to postsynaptic neurons (synaptic plasticity) [7–9]. Lipid intermediates and lipid modification play roles in signaling pathways related to cell differentiation and in modulating the activity of trophic factors and receptors [1].

Nerve cells are excitable cells with unique properties in transferring information. In order to do so, the membranes of nerve cells are equipped with highly selective pores or ion channels for sodium, potassium, calcium and chloride ions. These channels are critical for membrane excitation and propagation of action potentials. Ion channels are responsive to changes in voltage (voltage gated channels), binding of a chemical (ligand gated channels) or mechanical perturbation.

Channelopathies, disorders of ion channels, are resulting from disturbed ion channel function due to problems with ion channel subunits or regulation of the ion channels [10]. The rapidly growing field of channelopathies started with the discovery of voltage gated channelopathies that result in inherited muscle disease due to mutations in a subunit of the sodium channel or a mutation in a gene coding for a chloride channel in skeletal muscle [10]. Channelopathies have also been identified for ligand gated ion channels due to mutations of a subunit of the glycine receptor or a subunit of the nicotinic acetylcholine receptor [11, 12]. The underlying reasons for channelopathies can be traced back to either inherited causes (congenital, resulting from one or more mutations in the genes encoding the ion channel) or acquired causes such as toxins and autoimmune attack on an ion channel.

4. Neurotransmitters and neuropeptides

The best known neurochemicals are neurotransmitters and neuropeptides since they modulate brain function [1–4]. One set of neurotransmitters is formed by common amino acids such as glutamate, gamma-aminobutyric acid (GABA) and glycine. These amino acids have a number of functions throughout the body. In nerve terminals of neurons, they are packaged and stored in secretory or synaptic vesicles, so they can be released by exocytosis in a calcium dependent manner. The vesicular membrane is recycled, i.e., endocytosed, for future synaptic release cycles. Glutamate is the most prominent excitatory neurotransmitter. It is released at excitatory synapses, and evokes membrane potential depolarization and, possibly, firing of action potentials in the connected postsynaptic cell. In contrast, GABA is the best known inhibitory neurotransmitter. Its action results in reducing neuronal excitability. Glycine is another inhibitory neurotransmitter found in the spinal cord, brainstem and retina. The monoamines form an important group of neurotransmitters involved in regulation of emotion, arousal, some forms of memory as well as sensory processing [1–4, 13, 14]. Because of their functional roles, drugs are used to regulate their effects in patients with psychiatric as well as neurological disorders [15]. As their name implies, monoamines contain an amino group connected to an aromatic ring by a two-carbon chain. The enzymes monoamine oxidases terminate the action of monoamines. Histamine, serotonin, dopamine, epinephrine (adrenaline), norepinephrine (noradrenaline) are monoamines. The latter three are also grouped together as catecholamines because they contain a catechol group. Trace amines such as octopamine, tryptamine, tyramine, phenethylamine and others, have been identified as neurotransmitters. Neuropeptides include compounds such as oxytocin, substance P, somatostatin, opioid peptides, cocaine and amphetamine regulated transcript (CART), glucagon, orexin, dynorphin, endorphin, enkephalin, neuropeptide Y, neuropeptide S, and others. Nitric oxide, hydrogen sulfide and carbon monoxide act as gaseous neurotransmitters [16]. These neurotransmitters are synthesized de novo in nerve cells and because of their chemical nature are able to rapidly diffuse through the plasma membrane to act on neighboring cells. Acetylcholine is released in the autonomic nervous system and also from motor neurons at the neuromuscular junction to evoke skeletal muscle contraction. Chemically, acetylcholine is an ester of acetic acid and choline. Endogenously produced cannabinoids (endocannabinoids) such as anandamide differ from the above mentioned neurotransmitters because they are formed from membrane lipids and are essentially lipids. They can be rapidly synthesized on demand from the cell membrane and released nonsynaptically and not from synaptic vesicles as the classic neurotransmitters, reviewed in [9, 17, 18]. Endocannabinoids bind to cannabinoid receptors on presynaptic neurons to regulate presynaptic neurotransmitter release. Therefore, endocannabinoids together with the

gaseous neurotransmitters are unusual neurotransmitters [17, 19, 20]. One key distinction of these novel neurotransmitters is the fact that they act as retrograde messengers at synapses and presynaptically regulate either glutamatergic or GABAergic synapses to alter release-probability in synaptic plasticity. Gaseous neurotransmitters and endocannabinoids have been shown to have a functional role in experience-dependent activity and mediate a variety of forms of short- and long-term synaptic plasticity [21–24].

5. Factors that influence neurochemistry

What are some of the factors that affect the chemistry of the nervous system? Factors that modify neurochemistry include sensory stimuli, environmental signals such as recreational drugs, pharmaceuticals and toxins, and bodily changes such as aging and disease. Listed below, and described in more detail, are examples of some such factors known to influence neurochemistry. It is important to realize that this list is not exhaustive, and that in theory almost any external stimulus or internal state could influence neurochemistry.

5.1 Sleep

Sleep is controlled by circadian rhythms, which have a neurochemical (and oscillatory epigenetic) basis. During waking, several brain structures participate, namely the basal forebrain, posterior and lateral hypothalamus, and nuclei in the tegmentum and pons. Neurotransmitters that act as significant wakefulness factors are acetylcholine and monoamines, glutamate and hypocretin/orexin. Conversely, the preoptic/anterior hypothalamic area regulates active sleep mechanisms, and sleep is promoted by GABA and peptide factors, including growth hormone-releasing hormone, cytokines, and prolactin [25]. Adenosine is a significant homeostatic factor acting in basal forebrain and preoptic areas via A1 and A2A receptors. Lack of sleep increases inducible nitric oxide synthase in the basal forebrain, which causes adenosine release and recovery sleep. Also, many genes have been found differentially expressed in wakefulness versus sleep, and they relate to neural transmission, energy metabolism, stress protection, and synaptic plasticity [25].

5.2 Exercise

There has recently been a large amount of research into the neurochemical changes that occur during and after exercise, finding that it stimulates the increase of many chemicals, namely lactate, cortisol, neurotrophins, including BDNF, VEGF and IGF-1, neurotransmitters, including dopamine, serotonin, norepinephrine, GABA, acetylcholine, and glutamate, and neuromodulators, including endocannabinoids and endogenous opioids [26]. However, it should be noted that many of these alterations have been demonstrated only peripherally, and gaps still exist in our knowledge as to exactly where these changes occur in the brain. Therefore, further work is needed to link the exercise-induced changes in peripheral levels to central levels, and to understand how these chemicals are involved in the exercise-induced changes in cognition, mood, and so forth [26].

5.3 Diet

The scientific field concerned with the effects various contents of the diet such as macronutrients, and micronutrients such as minerals, vitamins, dietary

supplements, and food additives have on neurochemistry is called "nutritional neuroscience." Recent research on nutrition and its effect on the brain show that it is involved in almost every aspect of neurological function, modulating neurotrophic factors, neural pathways, neurogenesis, and neuroplasticity [27]. This is not surprising when we consider that the brain consumes a very large amount of energy relative to the rest of the body. Specifically, the human brain is approximately 2% of the body mass but uses up to 25% of the energy input. Therefore, mechanisms involved in the transfer of energy from foods to neurons are likely to be essential to the control of brain function. Furthermore, insufficient intake of certain vitamins and other cofactors, or the consequences of metabolic disorders such as diabetes, affect cognition by altering processes in the body that are associated with the management of energy and synthesis of neurotrophic and neuroendocrine factors (i.e., BDNF and IGF-1) as well as neurotransmitter in neurons, which can subsequently affect neurotransmission, synaptic plasticity, and cell survival [27].

5.4 Stress

Stress has been defined as a brain-body reaction to stimuli from the environment or from internal states that are interpreted by the body as disrupted homeostasis [28]. The response to such stress involves both the activity of different neurotransmitters in the limbic system, and the response of neurons there to other chemicals and hormones, mainly glucocorticoids, released from the adrenal cortex. Thus, body-brain integration probably plays a major role in the stress response [28]. Specifically, acute stress is correlated with alterations of neurotransmitters such as dopamine, acetylcholine, GABA and glutamate in areas of the brain associated with the regulation of stress responses. These areas include the prefrontal cortex, amygdala, nucleus accumbens, and hippocampus. Glucocorticoids also play an important role, and interact with several neurotransmitters in those same areas of the brain. Also, the actions of neuromodulators released from peripheral organs such as the liver (IGF-1), pancreas (insulin), or gonads (estrogens) play a role [28]. A permanent increase in the baseline levels of glucocorticoids arising from a stressful lifestyle could exacerbate neuronal damage that occurs in the above areas of the brain during aging. Conversely, stress reduction may have an anti-aging effect [29].

5.5 Meditation

One way to counteract stress is through practices such as meditation and yoga. These techniques have recently received increased attention due to the accumulation of research showing both direct and indirect benefits [30]. Based on studies conducted so far, it has been found that the practice of meditation influences the levels of neurotransmitters such as GABA, serotonin, dopamine, and norepinephrine, in a way that positively affects psychological disorders such as anxiety. Also, by reducing baseline levels of stress hormones and neurotransmitters, meditation may act as a form of preventative medicine [30].

5.6 Alcohol

Alcohol has effects on many neurotransmitters in the brain. Its major effect is to stimulate the release of GABA, and it acts principally at the GABAA receptors, and thereby has sedative effects [31]. It also inhibits postsynaptic NMDA excitatory glutamate receptors, and this inhibition further contributes to the sedation.

However, alcohol also has euphoric effects, and these are more related to increases in dopamine. The effects on dopamine are also thought to be involved in alcohol craving and relapse. In addition, alcohol alters opioid receptors and can lead to a release of β-endorphins. Additional important effects include increased serotonin and decreased nicotinic acetylcholine receptors [31].

5.7 Recreational drugs

Drugs can alter the regular functions of neurochemicals, inhibit the way they are supposed to act, or disrupt their communication [32]. At first, pleasure is usually increased, but cognitive ability and rationality are decreased. Psychomotor stimulant drugs like amphetamines, methamphetamine, and cocaine cause an overproduction of neurotransmitters, principally the monoamines dopamine and norepinephrine, and may also prevent them from being reabsorbed, causing an abnormally large amount to be present in synapses, and thereby activate the mesolimbic dopamine system. Drugs like ecstasy (3,4-methalynedioxymethamphetamine) similarly interfere with the transmission of serotonin, and the way it is transported along neural pathways. Other drugs, such as heroin, opioids, and marijuana, mimic endogenous brain chemicals and bind to receptors as agonists, activating the neurons and thus disrupting the natural transmission and production of neurotransmitters [32]. With repeated drug abuse, the brain can be rewired via neuroplasticity as it attempts to maintain chemical homeostasis [33].

5.8 Neurodegenerative diseases and aging

Studies of the neurobiology of aging are beginning to uncover the mechanisms underlying not only the physiology of aging of the brain, but also the mechanisms that make people more vulnerable to cognitive dysfunction and neurodegenerative diseases [29]. Neurotransmission is impaired in age-related disorders, such as Alzheimer's and Parkinson's diseases, which has stimulated investigations into the neurochemistry of the aging human brain. Out of all the neurotransmitter systems studied, age-related changes in the serotonergic, cholinergic, and dopaminergic systems are the most reliably found [34]. The dopamine system in particular, is especially vulnerable to aging [35]. The association of these neurotransmitters with mood, memory, and motor function may contribute to age-associated behavioral changes and predispose older people to age-related diseases. Moreover, age-related neurodegenerative diseases may evolve from the interaction between defects in specific neurochemical mechanisms and other pathophysiologic processes [33].

Acknowledgements

This work was supported in part by grants from the National Science Foundation (NSF IOS-1355034) and the Charles and Mary Latham Trust Fund to TH and from the National Institutes of Health (NIH) to ABC.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this chapter.

DOI: http://dx.doi.org/10.5772/intechopen.89072

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