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Chapter

Introductory Chapter: Biogenic Amines in Neurotransmission and Human Disease from the Endocrinologist's Perspective

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1. A synopsis of the normal physiology of neurotransmission in man

There are about 10^{11} neurons and 10^{14} synaptic connections in the human brain. The neural circuitry is continuously sculpted in response to experience, modified as we learn and store memories, and irreversibly altered by the gradual loss of neurons and connections as we age [1].

Neuronal signals are transmitted from cell to cell at synapses. When an action potential arrives at the presynaptic site, the depolarization of the membrane opens voltage-gated calcium channels that are clustered in the presynaptic membrane. Calcium influx triggers the release of neurotransmitters which are stored in membrane-enclosed synaptic vesicles and released by exocytosis. The neurotransmitter provokes an electrical change in the postsynaptic cell by binding to and opening transmitter-gated ion channels. After the neurotransmitter is secreted into the synaptic cleft, it is rapidly removed: it is either destroyed by specific enzymes in the synaptic cleft or taken up by the presynaptic nerve terminal or by surrounding glial cells. Reuptake is mediated by a variety of Na^+-dependent neurotransmitter symporters. The cycling of neurotransmitters allows cells to keep up with the high rates of release [1–3].

The chemical or electrical synapses can be excitatory or inhibitory. Excitatory neurotransmitters open cation channels, causing an influx of Na^+ and also Ca^+ in many cases, which reduces the threshold to fire an action potential. Inhibitory neurotransmitters open Cl^- or K^+ channels, thereby making it difficult to depolarize the cell membrane. Depending on the secretion milieu, the type of the receptors they bind to, and the ionic conditions that they encounter, transmitters may be either inhibitory or excitatory. For example, acetylcholine may have inhibitory or excitatory effects depending on the type of the receptor it binds to. Usually glutamate and serotonin are excitatory, whereas γ-aminobutyric acid and glycine are inhibitory [1–4]. All neurotransmitter receptors fall into one of these classes based on their signaling mechanisms:

1. Ionotropic receptors—ion channels present at fast chemical synapses. Example: acetylcholine receptor of skeletal muscle cells is a transmitter-gated ion channel which is opened transiently by acetylcholine released from the nerve terminal at a neuromuscular junction.

2. Metabotropic receptors—also called G protein-coupled receptors. Signaling via is these receptors is somewhat slower, more complex, and longer lasting in its effects. For example: hormones such as parathyroid hormone operate via G protein-coupled receptors [1].

Biogenic amines such as dopamine, norepinephrine, serotonin, and histamine manifest their effects either directly or indirectly via their specified receptors [1].

2. Biogenic amines in human disease

Any dysfunction that occurs in the aforementioned physiological setups in the organism may be associated with a disease state, mostly with neurological consequences, and therapy is aimed at inducing the recovery of the dysfunctional pathway via drugs or, most recently, the gene therapy, which is elaborating groundbreaking results [5].

Disorders of neurotransmission in the human are either due to the lack of synthesis of the neurotransmitter, disordered synapse due to external insults such as trauma, autoimmunity, or impaired or enhanced receptor-ligand interaction at the postsynaptic area. The list of the neurogenerative diseases, the inborn errors of metabolism associated with dysfunctional neurotransmission, is not exhaustive and is discussed elsewhere [6].

From the endocrinologist's perspective, excess of biogenic amines includes many rare endocrine neoplasias such as pheochromocytomas (PHEO) and paragangliomas (PGL). The carcinoid syndrome, a constellation of clinical symptoms of biogenic amine excess particularly of serotonin, is much rarer in clinical practice, and it is usually observed in the context of clinically manifest neuroendocrine tumors, such as midgut carcinoids. In the pediatric patient, these syndromes of *amine excess* are usually associated with hereditary syndromes of endocrine neoplasia, such as von Hippel-Lindau disease and multiple endocrine neoplasia (MEN) type 2 syndrome, whereas sporadic cases are more common in the adult [7]. The diagnosis of *amine excess* states is challenging since single measurement of the culprit molecules via standard laboratory tests is often inconclusive and full of caveats that mandate repeat measurements of the suspected amines and/or their metabolites. Below is a brief description of catecholamine excess related tumors as an example to how *biogenic amine excess* may relate to human disease.

Pheochromocytomas and paragangliomas (PGL) are uncommon neuroendocrine tumors of neural crest origin, with the former being of adrenal medulla origin and the latter originating from sympathetic and parasympathetic system. All functional PHEO/PGL produce and metabolize catecholamines and contain chromaffin tissue, which refers to the brownish black color due to oxidation of catecholamines after staining with chromium salts. Pheochromocytomas comprise the majority of the tumors in the pediatric patient [7].

Dopamine, norepinephrine, and epinephrine are biogenic amines collectively referred to as catecholamines. These neurotransmitters and hormones are involved in regulation of numerous physiological processes and development of neuropsychiatric and cardiovascular diseases. They are synthesized from tyrosine, which is converted to 3,4-dihydroxyphenylalanine (DOPA) by the enzyme tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis. Decarboxylation and hydroxylation of dopa yield dopamine and norepinephrine, respectively. Norepinephrine is then converted to epinephrine via the enzyme phenylethanolamine N-methyltransferase.

The complex actions of norepinephrine and epinephrine are mediated by the G protein-coupled alpha- and beta-adrenergic receptors, whereas dopamine binds to a different class of metabotropic receptors.

The clinical presentation PHEO/PGL is variable. Owing to the neuroendocrine origin, they might co-secrete other hormones that result ectopic hormone excess, such as gigantism due to growth hormone-releasing hormone, hypercalcemia due to parathyroid hormone-related peptide, or secretory diarrhea due to vasoactive intestinal peptide. The clinical symptoms and signs of functional PHEO/PGL also depend on differences in catecholamine secretion and release as individual patient sensitivities to catecholamines. Signs of catecholamine excess include hypertension, headaches, palpitations, diaphoresis (less common in children), orthostatic hypotension, pallor, tremor, and anxiety. Depending on the location of the tumor, nonspecific signs and symptoms include blurred vision, abdominal pain, diarrhea, or behavioral problems/decline in school performance [7].

The diagnosis of excess catecholamine secretion due to PHEO/PGL has been facilitated by the development of assays sensitive to diagnose these entities; measurements of fractionated metanephrine and normetanephrine in plasma and urine are considered the primary diagnostic tests in the initial evaluation of suspected PHEO/PGL. An elevation of metanephrines greater than fourfold above the reference range is considered indicative of a catecholamine secreting tumor [8]. It should be noted that some PGL can be nonfunctional and may be diagnosed incidentally or due to clinical signs and symptoms owing to their anatomical position, as is the case in some paragangliomas of the head neck which arise from parasympathetic ganglia. Catecholamine-secreting tumors may be noradrenergic as in tumors associated with von Hippel-Lindau disease and familial PGL or adrenergic as seen in tumors that arise sporadically or in the context of MEN type 2 and neurofibromatosis type 1. Dopamine-secreting tumors are very rare and typically extra-adrenal succinate dehydrogenase-mediated paragangliomas. Measurement of methoxytyramine may be of help in this context, but the test is not widely available [9]. Chromogranin A is also another effective tumor marker that may correlate with tumor size and malignant potential.

Radiographic studies and in selected cases, molecular genetic testing should be planned once the diagnosis of catecholamine secreting tumor is highly considered. Further information on management of PHEO/PGL is discussed elsewhere [7].

The expanding knowledge on synthesis and function of biogenic amines may pave the path for enhanced medical treatment of disease states of owing to *biogenic amine excess*. Recent studies have also shown that biogenic amines have additional important roles as signaling molecules mediating the function of the "microbiota-brain-gut" axis [10]. The potential role of biogenic amines in this axis is an exciting new area of medicine that awaits for further studies.

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