

Neurotransmitters & Their Role in Health



This continuing education activity provides a brief review of the structure and functions of neurons and the nervous system. It also summarizes the current understanding of the roles of various neurotransmitters that regulate the body's homeostasis. Three general methods used to assess neurotransmitter activity are reviewed. Examples are provided to demonstrate how imbalances in urinary neurotransmitter levels correlate with clinical conditions, and how measuring urinary neurotransmitters can guide treatment decisions and help monitor the effectiveness of specific treatments.

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Instructions

Participation in this Continuing Medical Education activity should be completed in approximately 1 hour. To complete this CD-ROM program successfully and receive credit, participants must follow these steps:

1. Read all of the CME information at the beginning of the program.
2. Review the entire presentation.
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Sponsorship Information

- This activity is joint sponsored by Jespersen & Associates and Medical Education Collaborative (MEC). MEC is a non-profit that has been certifying quality educational activities since 1988.



Program Purpose Statement

- This program will provide physicians with the information they need to recognize and understand neurotransmitter function, and how they affect a patient's health. It introduces physicians to the role of neurotransmitters in health, and how certain medical conditions can be helped by addressing these chemical imbalances in the body.
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Learning Objectives

Target Audience

This program is intended for primary care physicians and other healthcare professionals who are treating patients with depression, fatigue, aggression, addictions, compulsive behavior, ADHD and ADD, anxiety, epilepsy, insomnia, Parkinson's and other medical conditions that are affected by neurotransmitter imbalances.

Learning Objectives

1. Explain the structure and function of neurons and the nervous system
 2. Explain the role of neurotransmitters in the nervous system and the process of neurotransmission
 3. Differentiate inhibitory and excitatory neurotransmitters
 4. Describe the importance of neurotransmitter homeostasis in health
 5. Identify stressors that affect neurotransmitter levels
 6. State the methods used to measure neurotransmitter levels
 7. Specify the correlation between urinary neurotransmitter levels and clinical conditions
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Term of Offering

- This CD-ROM program, with a release date of January 1, 2008, is valid for one year. Requests for credit must be received no later than February 2009.
- This program was developed by Jespersen & Associates, LLC in Boston, Massachusetts.
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- This activity is supported by an unrestricted educational grant from NeuroScience, Inc.

Requirements

- In order to view and successfully complete this program, you will need Powerpoint software, and access to a printer to print out the post-test and evaluation.

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Disclosure

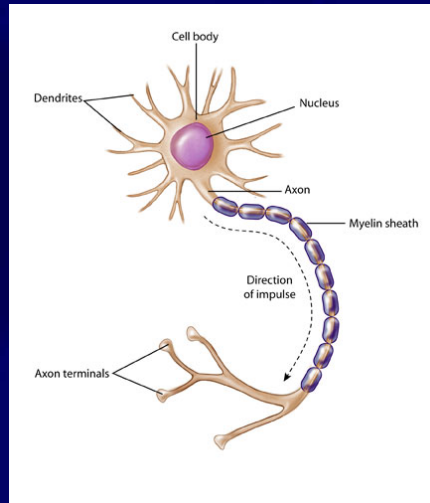
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Neurotransmitters & Their Role in Health

Neurotransmitters affect health in a variety of ways. Some patients suffer from chronic neurological or mood disorders that may be exacerbated by neurotransmitter imbalances--a fact of which many in the medical community are unaware. This program offers an overview of the nervous system and how neurotransmitters may be affecting your patients' health, in the hope that it will give you a better understanding of alternative methods of treating those symptoms.

Anatomy of a Neuron

- A specialized cell used for communication
- Consists of dendrites, a cell body and an axon



Neurons are specialized cells that send and receive messages to help the brain maintain homeostasis and provide normal body functions. Neurons use chemical messengers in a highly regulated electrochemical process to transmit information from one neuron to another or to effector cells, like muscle cells or gland cells. These chemical messengers are called neurotransmitters. ^{1,2,3}

A neuron consists of multiple dendrites, a cell body and an axon. These parts of the neuron will be discussed in detail in the next several slides.

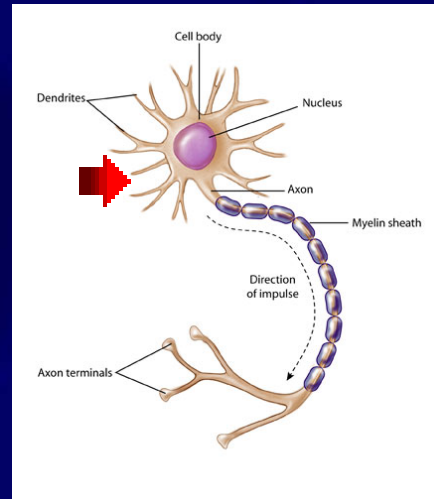
¹D Purves, D Fitzpatrick, SM Williams, JO McNamara, JA Augustine, LC Katz, A-S LaMantia. 2001. Neuroscience. Sinauer Associates, Inc. Sunderland, MA.

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Dendrites

- Short extensions of the neuron cell body
- Have receptors for chemical messengers
- Transmit electrical signals received from another neuron



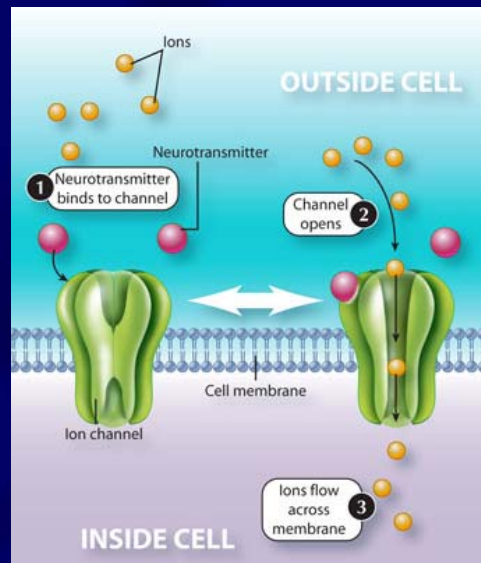
A dendrite is an extension of the plasma membrane close to the cell body of a neuron and it is usually less than 2 mm in length. Most neurons have multiple dendrites extending from the cell body. These dendrites provide a large surface area that is able to receive input from adjacent neurons or other cells. Dendrites are capable of receiving electrical as well as chemical input and transmitting this stimulus toward the cell body. To receive input from chemical messengers, dendrites use either ionotropic or metabotropic receptors. Ionotropic and metabotropic are general terms used to describe how the receptors work, which will be discussed next.^{1,2,3}

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Types of Receptors - Ionotropic



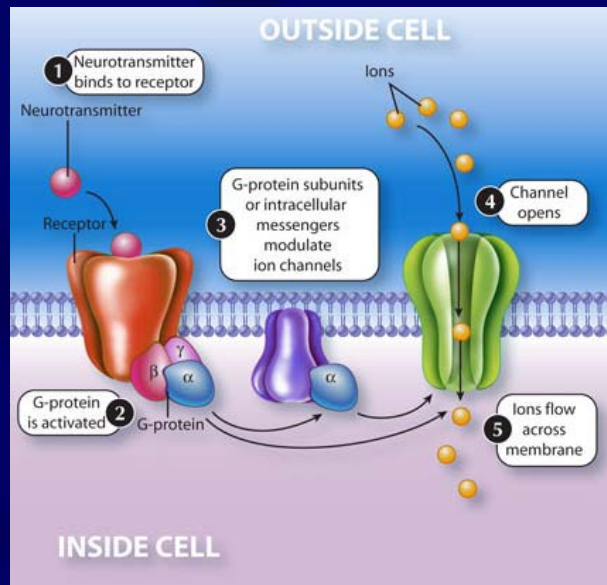
Ionotropic receptors are ligand-gated ion channels that regulate the influx of specific ions into the neuron. These receptors have two functional domains, an extracellular domain that binds to a ligand and a membrane-spanning domain that acts as an ion channel. When the ligand, a chemical messenger or neurotransmitter, binds to the receptor on the membrane of the dendrite, a channel opens that allows the influx of specific ions into the neuron. The types of ions that may pass through the ion channel depends on the type of neurotransmitter and the type of ion channel. Inhibitory neurotransmitters cause the influx of K^+ or Cl^- into the neuron, resulting in a membrane hyperpolarization. Excitatory neurotransmitters cause the influx of Na^+ or Na^+ and K^+ into the neuron, resulting in a membrane depolarization. Since ionotropic receptors rely on the influx of ions into the neuron, they are fast-acting receptors, with speeds of 0.1-2 milliseconds to induce a response.^{1,2,3}

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Types of Receptors - Metabotropic



Metabotropic receptors do not have an ion channel as part of their structure, but rely on the intermediate molecule, called a G-protein, to transduce the signal. Metabotropic receptors are usually monomeric proteins that have an extracellular ligand-binding domain and an intracellular domain that binds G-proteins. When a neurotransmitter binds to the receptor, a G-protein is activated and dissociates from the receptor. The G-protein then binds directly to an ion channel or to other effector proteins such as enzymes, which activate the enzyme to synthesize intracellular molecules that then bind to the ion channel. Since second messenger systems are used, metabotropic receptors are considered “slower-acting” receptors, with speeds of seconds to minutes to induce a response.^{1,2,3}

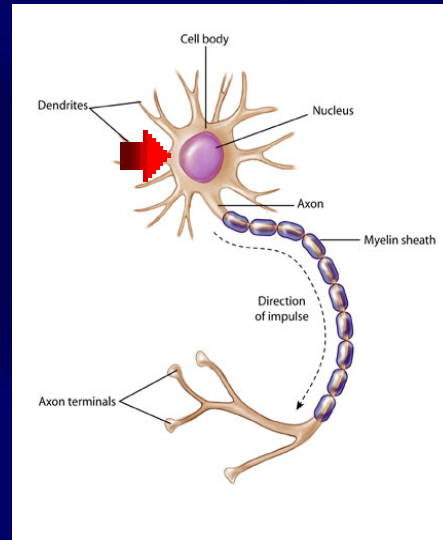
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Cell Body

- Contains the nucleus and cytoplasmic organelles
- The site of protein synthesis and processing, including synaptic vesicles



The cell body, while the smallest part of the neuron, is responsible for the production of all the components of the cell. It contains the nucleus and other major cytoplasmic organelles. The synthesis and processing of cellular proteins occurs within the cell body, and these proteins are then transported to their target locations within the neuron. The metabolic demands of the synthesis and processing of these molecules are high. In order to provide the required energy, the cell body contains a large number of mitochondria that provide the source of energy (adenosine triphosphate, ATP) used by the cell.

Of key importance, vesicular proteins are expressed, processed, and assembled in the cell body. These proteins are packaged in high concentrations within these vesicles, which are then translocated along the axon and released at the nerve terminal when the neuron is activated. Examples of such proteins include endorphins, oxytocin, gastrin and vasopressin. In addition to proteinaceous chemical messengers, neurotransmitters may also be peptide, biogenic amines, amino acids, or other small organic molecules.^{1,2,3}

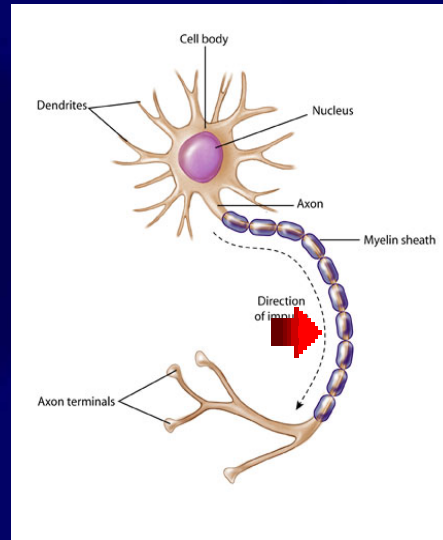
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Axon

- Hair-like cytoplasmic extension of the neuron
- Conducts electrical impulses or releases chemical messengers



The axon is a single hair-like, membrane-bound extension of the cytoplasm of the neuron. The axon is wrapped in a myelin sheath.

Axon terminals, which are projections from the axon, house synaptic vesicles. Synaptic vesicles may be either synthesized within the cell body and contain peptidergic neurotransmitters, or synthesized within the axon terminal and contain aminergic neurotransmitters, such as acetylcholine, glutamate, GABA, glycine, dopamine, or norepinephrine.

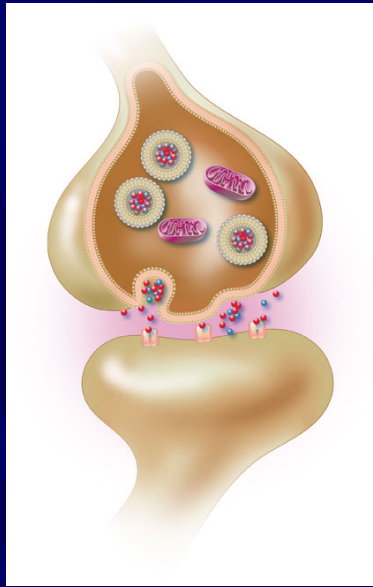
Once stimulated by an action potential, the axon terminal releases either type of the neurotransmitter by exocytosis. Exocytosis is a process whereby the membrane of the synaptic vesicle fuses with cell membrane of the axon terminal and the contents of the synaptic vesicle are expelled into the synapse. Once released into the synapse, the neurotransmitters diffuse through the synapse and bind to receptors on the postsynaptic neuron.^{1,2,3}

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Synapse



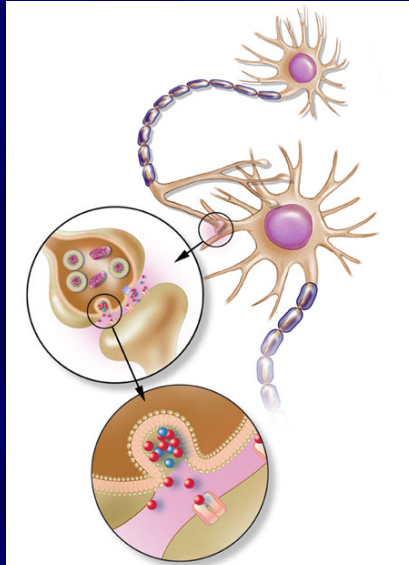
The synapse is the extracellular space in between the axon of a presynaptic neuron and the dendrite of a postsynaptic neuron. Neurotransmitters released from the axon terminal of the presynaptic neuron diffuse through the synaptic cleft and bind to receptors on dendrites of the postsynaptic neuron.^{1,2,3}

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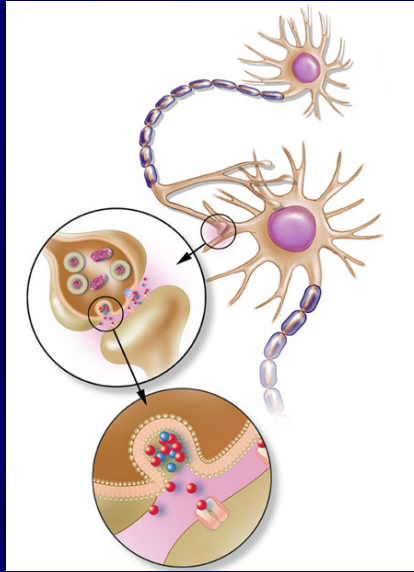
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How Does Neurotransmission Work?



The next series of slides describes how neurons communicate with one another. This process is called neurotransmission and involves a complex series of steps. Breakdowns in any one of these steps can lead to neurological problems, as will be discussed later.

Summary of Neurotransmission



Upon stimulation by an action potential, neurotransmitter-containing synaptic vesicles fuse with the cell membrane of the presynaptic axon terminal and release the contents of the synaptic vesicle into the synaptic cleft. The neurotransmitters diffuse through the synaptic cleft and bind to either ionotropic or metabotropic receptors in the cell membrane of the postsynaptic dendrite. Binding of the neurotransmitters to either receptor causes the generation of an electrical signal in the postsynaptic neuron, which now becomes a presynaptic neuron. This electrical signal or action potential is propagated to the axon terminal, where it causes the exocytosis of synaptic vesicles and the process continues.

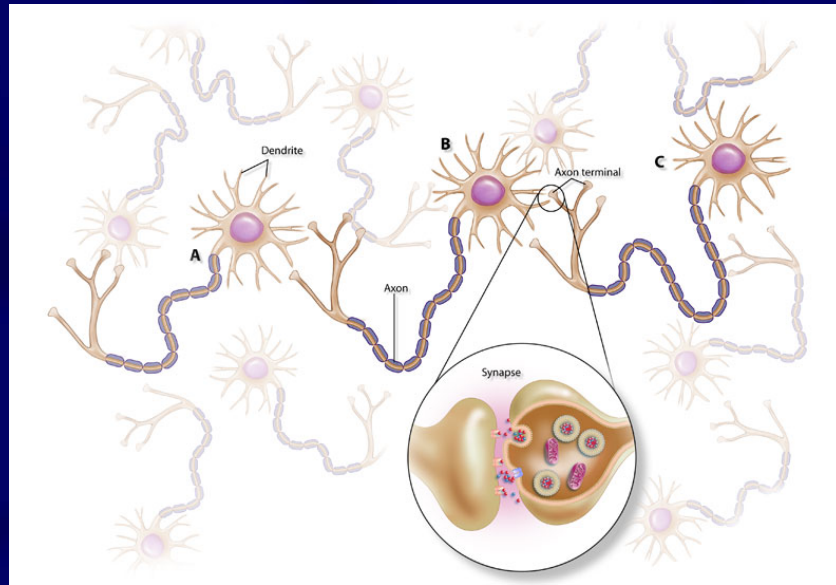
Rapid removal of the neurotransmitter from the synaptic cleft ensures that any newly-released neurotransmitter from a presynaptic neuron will bind to the receptor on the postsynaptic neuron. Neurotransmitters are removed from the synaptic cleft by several means, which depend on the type of neurotransmitter. Neurotransmitters can be enzymatically degraded or taken up by the presynaptic neuron and repackaged for use again.^{1,2,3}

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Neuronal Organization



This figure illustrates how neurons form synapses with multiple neurons. An action potential generated in one dendrite can be rapidly transferred along a neuron to the axon terminal where it stimulates the release of specific neurotransmitters. The neurotransmitters quickly diffuse through a synapse and are received by dendrites of multiple neurons to efficiently transfer electrochemical signals throughout the body. The response of a neuron will depend on the level of innervation by presynaptic axons. Up to 100,000 axons can innervate a single neuron.¹

The direction of signaling, type of signaling, and the neurotransmitter all depend on the class of neuron. Three major classes of neurons exist in the nervous system. These classes will be reviewed in the next series of slides.

¹D Purves, D Fitzpatrick, SM Williams, JO McNamara, JA Augustine, LC Katz, A-S LaMantia. 2001. Neuroscience. Sinauer Associates, Inc. Sunderland, MA.

Main Neuron Classes

- Sensory neurons
- Interneurons
- Motor neurons
 - Somatic motor division
 - Autonomic motor division
 - Sympathetic division
 - Parasympathetic division

Each of these neuron classes use various neurotransmitters to communicate the appropriate signals.

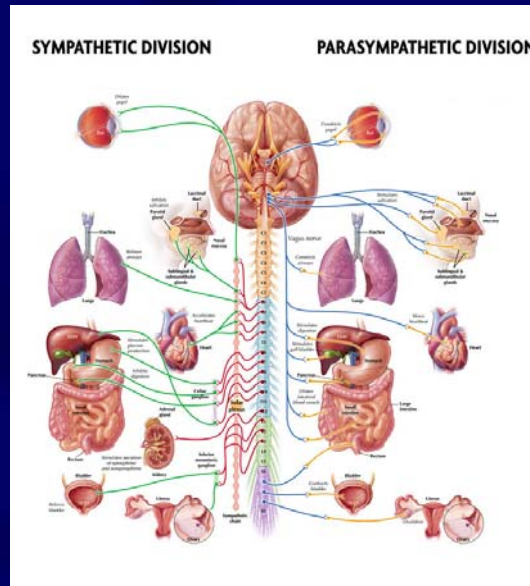
Sensory neurons convert environmental stimuli into electrical signals that are transmitted to the brain. Sensory neurons are located in clusters or ganglia near the spinal cord. Touch, odor, taste, sound, and vision are all functions that require sensory neuron input.

Interneurons are located entirely within the central nervous system and provide an essential link between sensory neurons and motor neurons.

Motor neurons transmit signals from the brain to muscle cells, gland cells or other effector cells. There are two types of motor neurons. Somatic motor neurons control reflexive and voluntary muscle movement while autonomic motor neurons control involuntary actions that are mediated by cardiac muscle, smooth muscle or glands. The autonomic motor division is further divided into sympathetic and parasympathetic divisions.¹

¹D Purves, D Fitzpatrick, SM Williams, JO McNamara, JA Augustine, LC Katz, A-S LaMantia. 2001. Neuroscience. Sinauer Associates, Inc. Sunderland, MA.

Autonomic Nervous System



The sympathetic division is responsible for the 'flight or fight' response. It mobilizes energy stores, increases cardiac output and dilates bronchial passages. It uses acetylcholine, epinephrine and norepinephrine.

The parasympathetic division of the autonomic nervous system conserves energy and increases intestinal and glandular activity. It primarily uses acetylcholine.¹

Using both electrical and chemical messengers, neurons in either the sympathetic or parasympathetic division can transmit signals over great distances (up to a 1 meter) or to adjacent cells. These chemical messengers are neurotransmitters. Through these complex interactions of neurotransmitters in sensory, motor and interneurons, normal body functions are maintained. Complications arise when defects in one of these systems affects other system.

¹D Purves, D Fitzpatrick, SM Williams, JO McNamara, JA Augustine, LC Katz, A-S LaMantia. 2001. Neuroscience. Sinauer Associates, Inc. Sunderland, MA.

Neurotransmitters

- Define a neurotransmitter
 - List some common neurotransmitters
 - Summarize neurotransmitter involvement in homeostasis
-

This next section will provide a definition of a neurotransmitter and list the criteria used to establish the classical neurotransmitters. Then, some of the common classical neurotransmitters will be identified and their roles in maintaining homeostasis will be summarized.

Neurotransmitter Criteria

- ✓ Must be produced & stored in the neuron
- ✓ Must be released when the neuron is stimulated (depolarized)
- ✓ Must bind to postsynaptic receptors & have a biological effect
- ✓ Must be inactivated by degradation, uptake and metabolism by an adjacent cell, or reuptake by the presynaptic neuron
- ✓ Must mimic endogenous activity by exogenous application to neurons

To be considered a neurotransmitter, the chemical messenger must satisfy the following criteria: the chemical must be synthesized and stored in a neuron, must be released when the neuron is stimulated, must bind to receptors in postsynaptic neurons and have a biological effect, and must be inactivated by enzymatic degradation, uptake and metabolism by an adjacent cell or reuptake by the presynaptic neuron. In addition, exogenous application of the neurotransmitter to a neuron must mimic the effects *in vivo*.

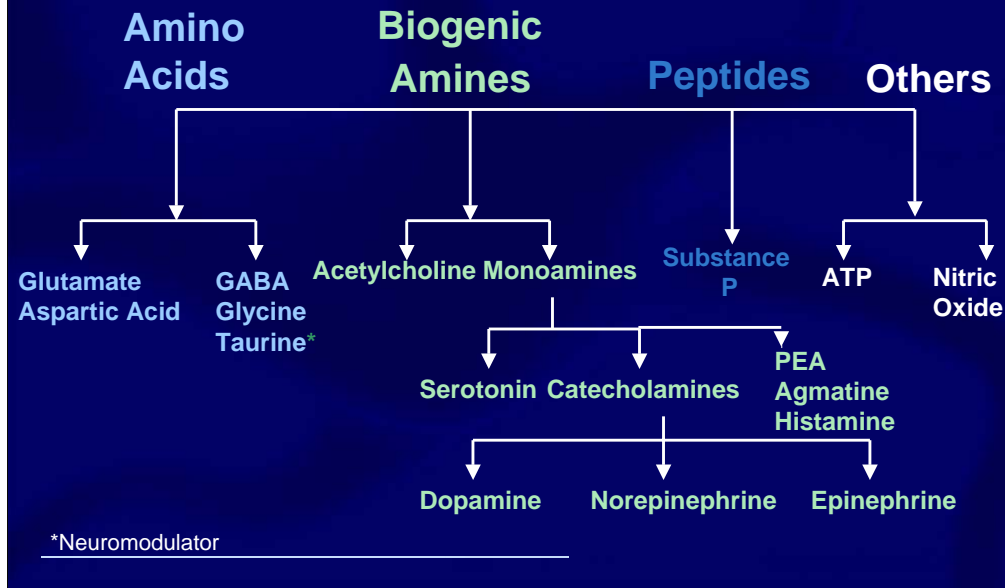
Chemical messengers that do not satisfy these criteria are considered putative neurotransmitters or neuromodulators. Such chemical messengers may affect the release or actions of classical neurotransmitters, but do not have a direct biological effect.^{1,2,3}

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Common Neurotransmitters



Neurotransmitters can be classified into various groups based on their structures. Listed are a few of the common neurotransmitters. These neurotransmitters are separated into aminergic, peptidergic, and other small-molecule groups.

We will next examine the role of these individual neurotransmitters in the body.

Aminergic Neurotransmitters

- Small molecules packaged in the axon terminal of a presynaptic neuron
- Are amino acids

Following is a brief review of the common aminergic neurotransmitters. These amino acids are packaged in the axon terminal of the presynaptic neuron. Most are involved in fast neurotransmission.

Glutamine

- Glutamine is an amino acid precursor to glutamate
 - Crosses the blood-brain-barrier
 - High levels may be a sign of inhibitory/excitatory imbalances in the neurotransmitter system
-

Glutamate

- Primary excitatory neurotransmitter
 - Most abundant neurotransmitter in CNS
 - About 30% of neurons use glutamate
 - Glutamate neurons are integrated into many circuits
 - Precursor for GABA
 - Synthesized from glutamine
 - Can be actively transported out of the brain
 - Does not cross the blood-brain barrier
-

Aspartic Acid

- Excitatory neurotransmitter
 - Vital for energy and brain function
 - Low levels in urine have been linked to feelings of tiredness and depression
 - High levels have been linked to seizures & anxiety
-

GABA

- Primary inhibitory neurotransmitter in the brain
 - About 1/3 of neurons in brain use GABA
 - Synthesized from glutamate
 - Functions
 - Maintains “Tonic Inhibition”
 - Prevents over-stimulation
-

Glycine

- Found in the brainstem and spinal cord
 - About ½ of inhibitory neurons in spinal cord use glycine
 - Synthesized from serine
 - Helps dampen effects of elevated excitatory neurotransmitters
 - Cofactor for NMDA-glutamate interactions
-

Taurine

- Considered a neuromodulator
- Inhibitory amino acid
- GABA receptor agonist - activates GABA receptors directly
- Importance
 - Preventing harmful effects of excess glutamate
 - Maintaining fluid balance
- Marker for proper heart function, liver toxicity, sleep problems, bile salt, and anxiousness

RJ Huxtable. *Physiological Reviews*. 1992;72:101-43.

Biogenic Amines

- Larger in size than amino acid neurotransmitters, but smaller than neuropeptides
- Alterations in activity implicated in a variety of psychiatric disorders
- Most psychotropic drugs target synthesis, packaging, or degradation

The properties of the biogenic amines fall between amino acids and neuropeptides in terms of synthesis, packaging and degradation. Since alterations in the levels of the biogenic amines have been implicated in a wide variety of psychiatric disorders, the biogenic amines have been the target of pharmacotherapies for more than 40 years.¹

¹D Purves, D Fitzpatrick, SM Williams, JO McNamara, JA Augustine, LC Katz, A-S LaMantia. 2001. Neuroscience. Sinauer Associates, Inc. Sunderland, MA.

Serotonin or 5-hydroxytryptamine

- Implicated in every type of behavior
- Primary neurotransmitter in the gut
- Synthesized from tryptophan via 5-HTP
- Integrates the functions of individual neurons
- Creates neural circuits capable of higher brain function

Serotonin is derived from the essential amino acid tryptophan. The conversion of tryptophan to 5-hydroxytryptophan is the rate limiting step in the synthesis of serotonin. Therefore, supplementation with 5-hydroxytryptophan results in higher levels of serotonin production than supplementing with an equivalent amount of tryptophan. Additionally, tryptophan must compete for transport across the blood-brain barrier with the other large-neutral amino acids, which include leucine, isoleucine, and others while 5-hydroxytryptophan freely crosses the blood-brain barrier.^{1,2,3}

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PEA *(Phenylethylamine)*

- A trace amine that acts as a neurotransmitter
 - Stored & released with other neurotransmitters
 - ADHD drugs Methylphenidate and Amphetamine and Dextroamphetamine increase urinary PEA levels 10x
 - ADHD patients that respond well have the greatest increases in PEA
 - Exercise increases PEA 2x (transient effect)
 - Antidepressant effect
 - PEA is in chocolate
 - Proposed as a cause for chocolate cravings
-

Agmatine

- Inhibitory neurotransmitter that binds to imidazoline receptors and blocks the action of glutamate at NMDA receptors
- Important in preventing the harmful effects of excess glutamate
- Anti-inflammatory, helps protect from chronic neuropathic pain¹
- Low agmatine levels have been observed in:
 - Anxiousness, depression, and stress

¹S Regunathan JE Piletz. 2003 Regulation of Inducible Nitric Oxide Synthase and Agmatine Synthesis in Macrophages and Astrocytes. Ann. N.Y. Acad. Sci. 1009: 20–29.

Histamine

- Excitatory neurotransmitter
 - Synthesized from histidine
 - Modulates epinephrine & norepinephrine
 - Implicated in arousal and attention
 - Increases during inflammation
 - Inflammation depletes tryptophan and serotonin
-

Catecholamines

- Synthesized from tyrosine
- Contain a catechol moiety

Catecholamines are biogenic amines that are synthesized from tyrosine and contain a catechol moiety. These small molecules are involved in a variety of body functions as will be described in the following slides.

Dopamine

- Both an excitatory and inhibitory neurotransmitter
 - Dopamine binds to stimulatory & inhibitory receptors
 - Involved in muscle control, motivation, reward, reinforcement
 - Behavioral effects
 - Can be replicated by amphetamines or dopamine agonists
-

Norepinephrine (noradrenalin)

- Involved in regulation of sleep and wakefulness, attention and feeding behaviors
 - Part of stress response
 - Important in:
 - Neural regulation
 - Integration of neural circuits
 - Influencing many areas of the brain
 - Sources:
 - CNS
 - Autonomic
 - Cardiac
 - Adrenal
-

Epinephrine (adrenalin)

- Present in brain at lower levels than NE
 - Adrenal production is part of stress response
 - Adrenal gland is the primary source
 - Formed by PNMT (phenylethanolamine-n-methyltransferase)
 - Endogenous cortisol increases PNMT
-

Excitatory and Inhibitory Neurotransmitters

Inhibitory

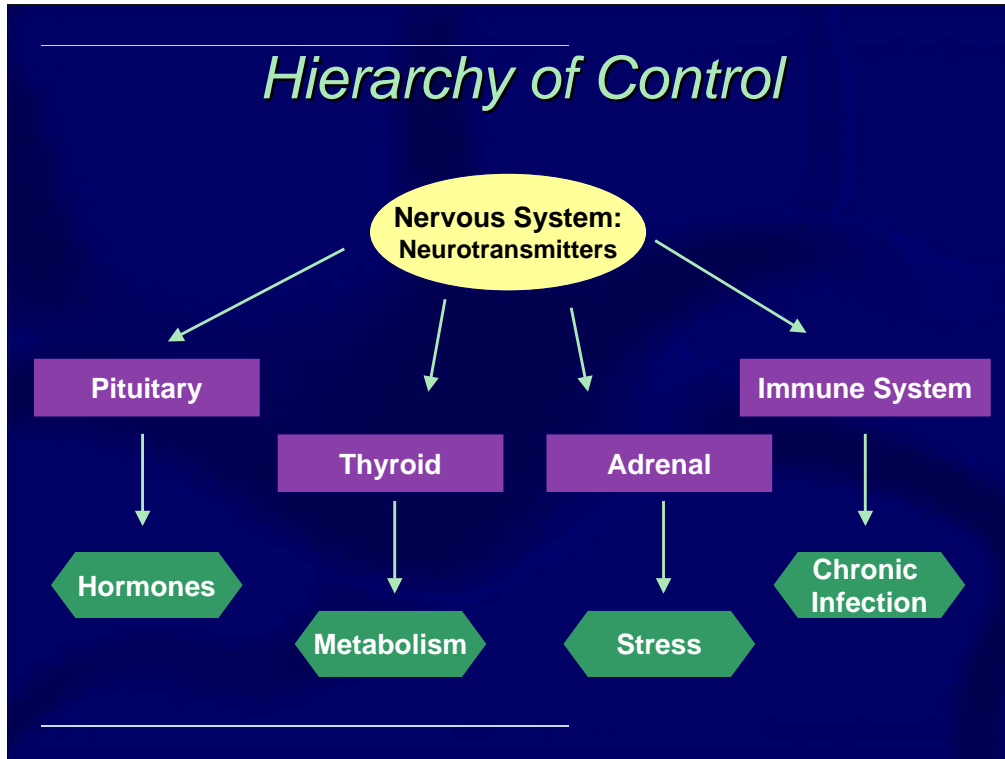
GABA
Serotonin
Glycine
Taurine*
Dopamine
Agmatine

Excitatory

Glutamate
Epinephrine
Norepinephrine
PEA
Histamine
Aspartic Acid
Dopamine
Glycine

*Neuromodulator

Neurotransmitters can also be classified based on their function, whether they induce an excitatory or inhibitory response. Abnormalities in neurotransmitter synthesis, receptor binding, or removal can lead to specific clinical conditions.



This slide provides a brief summary of some of the systems that require neurotransmitter activity. Since the same neurotransmitter may be used in multiple systems, an imbalance of a neurotransmitter in one system may affect other systems in the body, such as the endocrine system, metabolism, stress responses, and the immune system.¹

¹E Charmandari, C Tsigos, G Chrousos. 2005. Endocrinology of the stress response. *Annu Rev Physiol.* 67:259-84.

Alterations in Neurotransmitter Systems

- **Too much neurotransmitter**—resulting from NT hyperstimulation, increased NT synthesis, or defects in NT receptor binding or NT degradation/removal
 - **Not enough neurotransmitter**—resulting from decreased NT synthesis, or defects in NT degradation/ removal or NT receptor binding
-

The effects of excessive neuron activity apply to both the excitatory and inhibitory neurotransmitters. Very high levels of excitatory neurotransmitters can lead to symptoms such as hyperactivity, anxiety, and insomnia. Likewise, excessive inhibitory neurotransmitter levels can sedate the system, potentially leading to fatigue, sleepiness, and lack of motivation.

The lack of neuron activity can also lead to problems. Low output of the excitatory neurotransmitters can lead to fatigue, sleepiness, and lack of motivation whereas low inhibitory activity leads to excessive excitatory output-hyperactivity, anxiety, and insomnia.

Causes of Neurotransmitter Imbalances



High levels of stress or emotional trauma



Dietary habits



Neurotoxins



Genetics

Van Konynenburg, Richard A. *Is Glutathione Depletion and Important part of the Pathogenesis of Chronic Fatigue Syndrome?* Oct 2004 <http://phoenix-cfs.org/GluAACES04.htm>

Imbalances in neurotransmitter systems have been attributed to several causes. These include stress, diet, environmental toxins and genetics.

Stress is considered one of the primary sources of neurotransmitter imbalance. Stress can lead to increased neurotransmitter activity and/or turnover. Chronic stress taxes the nervous system over time and may lead to a depletion of neurotransmitter stores.

Dietary habits may influence neurotransmitter levels. High carbohydrate or high fat diets may not provide sufficient levels of essential amino acids to act as precursors for some neurotransmitters.

Many neurotoxins are lipid soluble and able to cross the blood-brain barrier. Storage within the brain may lead to cell damage or death and may influence neurotransmission.

Genetic variation may influence neurotransmitter packaging, transport or removal from synapses.

Induced stress

- Neurotransmitter levels decreased in response to environmental stressors in socially isolated rats¹

Dronjak, S., Gavrilovic L., Brazilian J of Med & Biological Res. 2006; 39:785-790.

Few published reports have examined the influence of stress on neurotransmitter levels in humans. One study examined the effects of long-term social isolation on catecholamine stores in the hypothalamus, hippocampus, adrenal glands, and heart in rats. The effect of additional stressors, immobilization and cold stress, were also examined for both the socially isolated and control rats. Tissue levels of catecholamines were assessed via single isotope radioenzymatic assays.

The researchers found that catecholamine stores were decreased when the rates were exposed to stress. Socially isolated rats had 18% less norepinephrine in the hypothalamus and 20% less dopamine in the hippocampus than controls. The additional stress of immobilization resulted in a 39% decrease in the catecholamines in all tissues for control rats, while socially isolated rats did not show the decrease in the hypothalamus. Cold stress resulted in no change in hypothalamic levels, but a 20% decrease in dopamine in the hippocampus as well as decreases in norepinephrine in the adrenal gland and epinephrine in the heart auricles. ¹

Dronjak, S., Gavrilovic L., Brazilian J of Med & Biological Res (2006) 39:785-790.

Poor Diet

- Rats fed a high carbohydrate diet had reduced ability to deal with stress

Physiol Behav. 2001. 73(3):371-7.

Rats were fed either high fat (HF) or high carbohydrate (HC) diets for 2 months and then exposed to both physiological and psychological stressors. The result was a decrease in body temperature in both groups; however, HF rats recovered more quickly. Other effects were decreased activity and increased body weight gain, which was more prevalent in HC rats. Two weeks after stress removal, HC rats exhibited hyposensitivity of the serotonin receptor. This article demonstrates the debilitating effects of high carbohydrate diets on the ability to deal with stressful situations and on serotonin.¹

¹Physiol Behav. 2001, 73(3):371-7

Toxic Exposure

- Ammonia-induced neurotoxicity increased release of dopamine and increased dopamine metabolism in rat striatum

Brain Res. 2003 Jul 11;977(2):290-3

Ammonia or NMDA were administered to the rat striatum, both of which led to the prompt release of dopamine. However, while NMDA decreases dopamine metabolism, ammonia increases it. Ammonia results in increased dopamine release and increased dopamine metabolism. Additionally, increased activation of NMDA receptors results in increased ammonia neurotoxicity.

¹Anderzhanova E, Oja SS, Saransaari P, Albrecht J. Brain Res. 2003 Jul 11;977(2):290-3.

Clinical Manifestations

- Aggression
- Addictions
- Violence
- ADD/ADHD
- Compulsive behaviors
 - Gambling
 - Drugs
- Depression
- Anxiety
- Epilepsy
- Insomnia
- Parkinson's
- Panic Disorders
- Compulsive behaviors
 - Overeating
- ADD/ADHD

Abnormalities in specific neurotransmission pathways can lead to a variety of clinical symptoms. For example, inhibition of histaminergic cells, which maintain wakefulness in healthy individuals, by GABAergic neurons induce sleep¹ so that abnormally high concentrations of histamine will create insomnia, while abnormally high concentrations of GABA will contribute to narcolepsy.

The treatment of the nervous system disorders is about balance. Most neurotransmitters can be placed into two categories, inhibitory and excitatory. If the scales tip in favor of the inhibitory system, symptoms such as fatigue and inability to focus can be issues. If scales tip in favor of the excitatory system, patients can develop issues such as anxiety and insomnia. Therapies for addressing inhibitory and excitatory imbalances also fall into the categories of inhibitory and excitatory.

In addition, the management of one clinical symptom by a specific therapy may influence the neurotransmitters involved in other systems due to the highly interconnected nature of neurotransmission, so measuring neurotransmitter levels becomes essential to providing effective symptom treatment.

¹JM Siegel. 2004. The neurotransmitters of sleep. J. Clin Psychiatr. 65(suppl 16):4-7

Methods to Determine Neurotransmitter Imbalances

- Serum, Plasma (Blood)
 - Cerebral Spinal Fluid (CSF)
 - Urine
-

There are three common means of assessing neurotransmitter levels. Measurement of neurotransmitter levels can be made from serum, cerebral spinal fluid, or urine. Each of these methods has both advantages and disadvantages that must be considered to determine the most appropriate method to assess neurotransmitter imbalances in patients.

Serum & Plasma

- No established target ranges
 - Influenced by venipuncture
 - Rapidly degraded
 - Invasive
-

The major advantage of a serum measurement is that they are typically well-accepted by the scientific community. The major drawback to these measurements is their invasive nature. Often times, this procedure leads to anxiety or nervousness in patients, which is a neurotransmitter response. The act of venipuncture will influence the levels of neurotransmitters. Therefore, obtaining true baseline levels may be difficult.

Cerebral Spinal Fluid (CSF)

- Invasive
 - No established target ranges
 - NT levels influenced by lumbar puncture
 - Possible complications
-

The major advantage of CSF is that it is typically well-accepted by the scientific community. However, like venipuncture, lumbar punctures are invasive procedures that directly affect neurotransmitter levels. In addition, the lack of established target ranges for the neurotransmitters in CSF makes the lab data difficult to interpret.

Urine

- One of oldest forms of medical testing¹
- Non-invasive
- Low associated stress

¹Haber MH, Pisse prophecy: a brief history of urinalysis. Clin Lab Med. 1988 Sep;8(3):415-30

Neurotransmitters and neurotransmitter metabolites are present in the urine. Since urine collection is non-invasive, it avoids the stress that venipuncture or lumbar puncture cause. Urine is also stable, allowing for more accurate analyses to be performed on samples. Either 24-hour urine testing or spot urine collection can be used for neurotransmitter testing.

Types of Urine Collection

24-hour collection

- Inconvenient collection process
- Represents a daily average, inability to detect circadian rhythm
- Can be influenced by renal disorders

Spot Collection

- Inexpensive
 - Easy to perform
 - Minimal degradation
 - Use second pass urine collected 2-3 hours after rising
-



Urinary Tests Available

Inhibitory Neurotransmitters	Excitatory Neurotransmitters	Both Excitatory and Inhibitory
GABA Serotonin Taurine Agmatine	Glutamate Epi Norepi PEA Histamine Aspartate	Dopamine Glycine Glutamine

Currently, there are several tests available to determine urinary neurotransmitter levels; however, optimal ranges for these neurotransmitters have yet to be determined empirically. This slide lists the inhibitory and excitatory neurotransmitters that can be measured in the urine. The following series of slides provides a summary of the physical manifestations of alterations in neurotransmitter levels as detected by urine testing.

Optimal Ranges for Urinary Neurotransmitters

Epi	8-12
NE	30-55
Dopa	125-175
Sero	175-225
Glycine	200-400
Taurine	150-300
GABA	1.5-4.0

Glutamine	150-400
Glutamate	10-25
Aspartic Acid	20-40
PEA	175-350
Histamine	10-25
Agmatine	1-2

- Spot urine collected 2-3 hours after rising.
- Ranges are reported in $\mu\text{g/gCR}$.¹

¹Data on file, NeuroScience, Inc. 2006.

While the optimal ranges for urinary neurotransmitter levels have yet to be established, some target ranges have been suggested based on data from 300-400 healthy males and females, who were 25-35 years old without clinical complaints, and who were not on any medications.¹

The next series of slides provides a summary of some physical manifestations resulting from the alterations of neurotransmitter levels as detected by urine testing.

¹ Data on file, NeuroScience, Inc. 2006.

Urinary Glutamate Levels

- High levels
 - Anxiousness
 - Depression
 - Huntington's disease
 - Lou Gehrig's disease
 - Alzheimer's disease
 - Seizure Disorders
- Low levels
 - Fatigue
 - Poor memory
 - Difficulty learning

Rev Bras Psiquiatr. 2005 Sep;27(3):243-8. Epub 2005 Oct 4.

Urinary GABA Levels

Symptoms of High and Low GABA levels

Low levels	High levels
Insomnia	Reduced inhibition
Fatigue	Anxiety
Restlessness or hyperactivity	Insomnia
Anxiety/panic attacks	Panic
Seizures	
Irritability	
Bi-polar/mania	
Low impulse control	

Physiol Rev. 2004 Jul;84(3):835-67.

Elevated urinary GABA is correlated with elevated excitatory neurotransmitter levels. High GABA levels are often seen in those with anxiety and insomnia. Panic is an excitatory symptom because a person panicking has high levels of excitatory neurotransmitters and GABA rises in response. A person suffering from fatigue often has low GABA levels, especially if they have depleted all neurotransmitters in their body.

Urinary Glycine Levels

- High levels
 - Anxiousness
 - Depression
 - Stress related disorders
 - Autism
 - ADD/ADHD

Curr Med Chem. 2000 Feb;7(2):199-209.

Urinary Serotonin Levels

- Low levels observed in:
 - Anxiousness
 - Fatigue
 - Sleep problems
 - Uncontrolled appetite/cravings
 - Migraine headaches
 - Premenstrual syndrome
 - Depression* (be careful)
- High levels observed in:
 - Hyperthermia
 - Shaking
 - Teeth chattering

<http://www.acnp.org/g4/GN401000045/CH.html>

Urinary PEA Levels

- Low levels
 - Depression
 - Fatigue
 - Cognitive dysfunction
 - ADHD
 - Autism
 - High levels
 - Schizophrenia
 - Phenylketonuria
 - Insomnia
 - Mental stress
 - Migraines
-

Urinary Histamine Levels

- Low levels
 - Depression
 - Fatigue
 - Antihistamine use
 - L-dopa therapy
 - High levels
 - Active allergy or inflammation
 - Stress
 - Serotonin depletion
 - Restlessness
 - Sleep disorders
 - Cigarette use
-

Urinary Dopamine Levels

- Low levels
 - Attention difficulties
 - Hyperactivity
 - Memory deficits
 - Increased motor movement (Parkinson's-like)
 - Poor fine motor control
 - High soy intake
 - Cravings
 - Addictions
- High levels
 - Paranoia
 - Stress
 - ADD/ADHD
 - Autism (high activity)
 - Initially high, later low
 - Addictions (blunted activity)

Physiol Rev. 1998 Jan;78(1):189-225.

Urinary Norepinephrine Levels

- Low levels
 - Poor memory
 - Reduced alertness
 - Somnolence
 - Fatigue/lethargy
 - Depression
 - Lack of interest
- High levels
 - Aggression
 - Anxiety/Panic
 - Increased emotionality
 - Mania
 - Hypertension
 - Vasomotor Symptoms of Perimenopause, Menopause and PMS

High levels of norepinephrine have been found in patients suffering from vasomotor symptoms of perimenopause, menopause and PMS. It is thought that this association is really a result of the level of NE relative to the level of serotonin.

Blum, I. et al. *Neuropsychobiology*. 2004;50:10-15.

De Sloover Koch Y, Ernst ME. *Ann Pharmacother*. 2004;38:1293-1296.

Fitzpatrick LA. *Mayo Clin Proc*. 2004;79:735-737.

Notelovitz M. *Mayo Clin Proc*. 2004;79:S8-S13.

Shanafelt TD et al. *Mayo Clin Proc*. 2002;77:1207-1218.

Urinary Epinephrine Levels

- Low levels
 - Poor concentration
 - Adrenal insufficiency
 - Chronic stress
 - Decreased metabolism
 - Fatigue
 - High levels
 - Anxiety
 - Insomnia
 - Stress
 - Hypertension
 - Hyperactivity
-

Urinary Neurotransmitter Testing Uses

- Identify imbalances that may contribute to a clinical condition
 - Guide treatment selection
 - Monitor treatment effectiveness
-

Urinary neurotransmitter testing can be used to identify imbalances that may contribute to a clinical condition, to guide treatment decisions, and to monitor treatment effectiveness. The following series of slides will demonstrate these concepts with examples from current literature.

Identify Imbalances

- Low urinary dopamine and serotonin levels were correlated with depression in breast cancer patients.¹
- Children with ADHD with or without anxiety may have increased noradrenergic activity when compared to children without ADHD.²

¹M Hernandez-Reif, G Ironson, T Field, et al. J Psychosom Res. 2004;57:45-52.

²S Pliszka. J Am Acad Child Adolesc Psychiatry. 1996;35:3.

In this study, urinary NE, EPI, dopamine and serotonin levels were measured in breast cancer patients with and without massage therapy treatment three times per week to enhance mood and reduce stress. The researchers found that the long-term effects of massage therapy included increased urinary dopamine and serotonin levels in women who reported reduced depression and hostility.¹

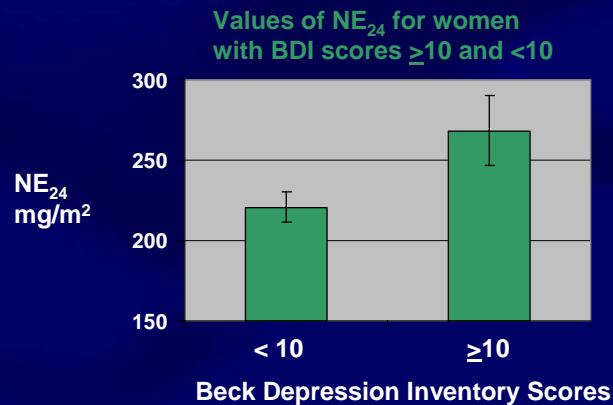
Children with attention-deficit hyperactivity disorder (ADHD) with and without anxiety were asked to complete a series of mentally stressful tasks. Urinary norepinephrine and epinephrine levels were measured during the 2-hour collection period. The researchers found that children with ADHD regardless of comorbid anxiety excreted higher levels of NE metabolites than children without ADHD, suggesting that the tonic activity of the noradrenergic system may be higher in children with ADHD. In addition, children with ADHD and anxiety excreted more EPI than children with ADHD without anxiety, suggesting that children with ADHD and anxiety may be differentiated from children without anxiety using the adrenergic system.²

¹M Hernandez-Reif, G Ironson, T Field, et al. 2004. Breast cancer patients have improved immune and neuroendocrine functions following massage therapy. J Psychosom Res. 57:45-52.

²S Pliszka. 1996. Catecholamines in Attention-Deficit Hyperactivity Disorder: Current Perspectives. J. Am. Acad. Child Adolesc. Psychiatry. 35:3.

Identify Imbalances

Elevated levels of urinary NE were associated with depression and anxiety in middle-aged women¹



¹JW Hughes, L Watkins, JA Blumenthal, C Kuhn, A Sherwood. J Psychosom Res. 2004;57:353-358.

In this study, self-reported symptoms of depression and anxiety were measured in middle-aged women. Depression was assessed using the Beck Depression Inventory and anxiety was assessed by the state anxiety portion of the Spielberger State-Trait Anxiety Inventory. Twenty-four hour urine samples were collected and assayed for NE and EPI. The researchers found that increased NE excretion was correlated with higher levels of depression and state anxiety and that depression and anxiety symptoms were unrelated to urinary EPI excretion.¹

¹JW Hughes, L Watkins, JA Blumenthal, C Kuhn, A Sherwood. 2004. Depression and anxiety symptoms are related to increased 24-hour urinary norepinephrine excretion among healthy middle-aged women. J Psychosom Res. 57:353-358.

Identify Imbalances

Table 1. PTSD and Depressive Symptoms in the PTSD Groups^a

Rating Scale	Range of Scores	Inpatients	Outpatients
Figley PTSD	4 - 48	30.9 ± 10.4	22.4 ± 10.7
IES total	7 - 61	40.4 ± 13.1 ^b	22.1 ± 17.7
Subscales			
Intrusive	3 - 33	22.8 ± 8.0 ^c	11.6 ± 8.7
Avoidance	1 - 38	18.1 ± 7.4	10.5 ± 12.1
HDRS	7 - 44	21.1 ± 11.8	18.0 ± 8.0

Urinary dopamine and norepinephrine, but not epinephrine levels, significantly correlated with severity of post-traumatic stress disorder symptoms¹ in male veterans.

^a Results are expressed as mean ± SD; ^b t = 2.6; df = 18; p = < 0.125; ^c t = 2.9; df = 18; p = < 0.008

[†] Due to missing data, only 14 (instead of 19) subjects were used in correlational analysis between catecholamine measures and Figley scores.

^{*} p < .0125 (When Bonferroni corrections are used, only results occurring with a probability of .0125 or less are considered statistically significant; ** p < .02; *** p < .05.

¹ R Yehuda, S Southwick, EL Giller, X Ma, JW Mason. J Nerv Ment Dis. 1992;180(5):321-5.

This study examined both in- and out-patients with PTSD as well as control patients. The investigators found that inpatients had significantly higher 24-hour urinary catecholamine excretion than outpatients or controls. However, PTSD patients (in- and out-patients) demonstrated elevated dopamine and norepinephrine excretion.

Table 1 shows that inpatients had more symptoms of PTSD than outpatients according to both the Figley PTSD interview, which assesses intrusive, avoidant and hyperarousal symptoms, and the Impact of Event Scale (IES). Inpatients were also more intrusive than outpatients. Depression levels did not vary between in and out house patients.

Identify Imbalances

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Table 2. Correlations among Catecholamines and PTSD and Depressive Symptoms

	Figley [†]	Total	Impact of Events Scale Intrusive	Scale Avoidant	HDRS
Dopamine	.59**	.63*	.68*	.49***	.12
Norepinephrine	.37	.58*	.59*	.46***	.01
Epinephrine	.49	.38	.27	.40	.15

^a Results are expressed as mean ± SD; ^b t = 2.6; df = 18; p = < 0.125; ^c t = 2.9; df = 18; p = < 0.008

[†] Due to missing data, only 14 (instead of 19) subjects were used in correlational analysis between catecholamine measures and Figley scores.

*p < .0125 (When Bonferroni corrections are used, only results occurring with a probability of .0125 or less are considered statistically significant; ** p < .02; *** p < .05.

¹ R Yehuda, S Southwick, EL Giller, X Ma , JW Mason. J Nerv Ment Dis. 1992;180(5):321-5.

Table 2 shows a significant correlation between IES scores and dopamine and norepinephrine urinary levels and intrusivity.

Identify Imbalances

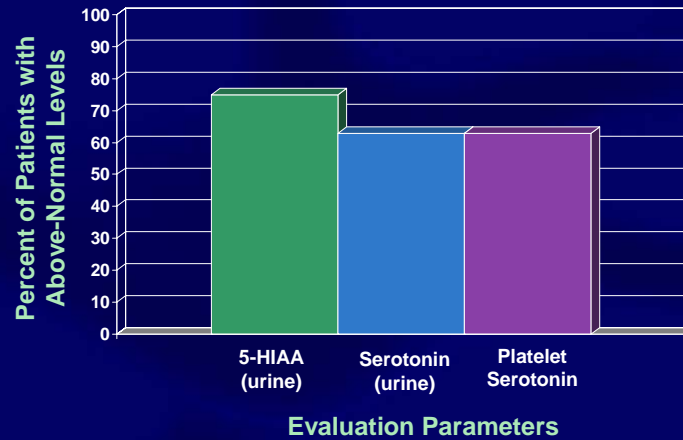
- Subjects with different manifestations of the metabolic syndrome
- Elevated urinary norepinephrine, and reduced epinephrine excretion were closely associated with general and central obesity¹

¹Lee ZS et al. *Metabolism*. 2001;50(2):135-43.

This study examined the correlations between various symptoms of metabolic syndrome in Chinese subjects and urinary norepinephrine and epinephrine excretion. It was found that patients with more components were more at risk for being obese, hyperglycemic, dyslipidemic, and albuminuric. This correlated with increased blood pressure, increased plasma insulin, increased insulin resistance, and increased 24 hour norepinephrine but decreased urinary epinephrine excretion.¹

ZS Lee, JA Critchley, B Tomlinson, RP Young, GN Thomas, CS Cockram, TY Chan, JC Chan. 2001. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. *Metabolism*. 50(2):135-43.

Guide Treatment Decisions



Measurement of urinary serotonin was equal to or better than platelet serotonin or urinary 5-HIAA for diagnosis of carcinoid tumor.¹

JM Feldman. Clin Chem. 1986;32:840-4.

5-hydroxyindoleacetic acid (5-HIAA) excretion in urine and platelet serotonin concentration along with urinary serotonin excretion were measured in 75 patients with carcinoid tumors. Of 75 patients with carcinoid tumors, 75% were found to have above-normal urinary 5-HIAA excretion, 64% had above-normal serotonin excretion, and 64% had above-normal platelet serotonin concentrations. Increased measures of urinary serotonin excretion were found in patients with carcinoid tumors than in controls. Outside administration of serotonin did not result in increased urinary serotonin excretion levels but 5-HIAA excretion levels did increase. This shows that urinary serotonin excretion is a reliable parameter in diagnosing carcinoid tumors.¹

¹JM Feldman. 1986. Urinary serotonin in the diagnosis of carcinoid tumors. Clin Chem. 32(5):840-4.

Monitor Treatment Effectiveness

Metabolites in Responders and Nonresponders at Baseline after Methylphenidate Treatment				
ADHD (n=22)				
	Responders to MPH Therapy (n=18)		Nonresponders to MPH Therapy (n=4)	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
PEA	22.97 ± 24.25	60.81 ± 60.02	19.85 ± 21.33	20.06 ± 18.70
MHPG	2.09 ± 0.67	2.04 ± 0.69	1.99 ± 0.53	1.97 ± 0.43
HVA	8.31 ± 6.52	6.26 ± 2.36	6.10 ± 4.21	3.85 ± 0.97
5-HIAA	4.31 ± 2.37	4.43 ± 3.07	2.99 ± 0.83	3.06 ± 0.55

ADHD = attention deficit hyperactivity disorder
 MPH = methylphenidate
 PEA = β-phenylethylamine (µg/g creatinine)

MHPG = 3-methoxy-4-hydroxyphenyl glycol (µg/g creatinine)
 HVA = homovanillic acid (µg/g creatinine)
 5-HIAA = 5-hydroxyindoleacetic acid (µg/g creatinine)

¹A Kusag , Y Yamashita, T Koeda, M Hirstani, M Kaneko, S Yamada, T Matsuishi. 2002. Ann Neurol. 52(3):372-4.

This study reported the urinary PEA levels from children with ADHD and treated with methylphenidate. Of 22 children with ADHD, 18 responded to treatment with methylphenidate and 4 did not. Responders had significantly higher urinary βPEA levels after methylphenidate therapy; nonresponders had no change in urinary PEA levels.¹ Children with ADHD who responded to methylphenidate had significantly elevated urinary PEA levels, while urinary PEA levels did not change in nonresponders. Metabolites of other neurotransmitters showed no change in response to methylphenidate for responders or nonresponders.

¹A Kusag , Y Yamashita, T Koeda, M Hirstani, M Kaneko, S Yamada, T Matsuishi. 2002. Increased urine phenylethylamine after methylphenidate treatment in children with ADHD. Ann Neurol. 52(3):372-4.

Summary

- Neurotransmitters are the chemical messengers
 - Maintenance of the proper balance of neurotransmitters is necessary for good health
 - Neurotransmitter imbalances have been implicated in disease
-

Currently, more than 100 neurotransmitters have been identified and shown to regulate almost every body function. Despite this diversity, neurotransmitters are broadly grouped into neuropeptides and small-molecule neurotransmitters. Small-molecule neurotransmitters are responsible for quick synaptic actions while neuropeptides control longer synaptic functions. Neurotransmitters are also classified based on their function, whether they induce an inhibitory or an excitatory response. The proper balance of neurotransmitters is required to maintain good health. Abnormalities in neurotransmitter synthesis, packaging, release, reuptake or removal have been implicated in a variety of conditions such as depression, anxiety, weight gain, and insomnia.

Summary

- Imbalances may result from stress, poor diet, neurotoxins, & genetics
 - Nervous system function can be assessed via urinary neurotransmitter testing
 - Restoring balance can lead to improvement in symptoms
-

In addition, imbalances in neurotransmitter levels may result from stress, poor diet, neurotoxins or genetics. One method to assess nervous system function is to measure urinary levels of neurotransmitters. Since urine testing is a low stress method, little effect on stress-related neurotransmitter levels will be detected so that a reliable estimate of neurotransmitter activity may be obtained. Understanding the relationship between urinary neurotransmitter levels and physical symptoms provides a means to help restore neurotransmitter balance and improve symptoms.

