Chapter 5

Catecholamines

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Introduction

1. Catecholamines
   neurotransmitters of this group share 2 chemical similarities: one core structure of catechol and an amine group (Figure 5.1).

5.1 Structural features of catecholamines

![Diagram of catecholamine structure]
Introduction

1. Catecholamines
neurotransmitters of this group share 2 chemical similarities:
one core structure of catechol and an amine group (Figure 5.1).

2. This group of neurotransmitters includes dopamine (DA),
norepinephrine (NE)/noradrenaline, and epinephrine (EPI)/adrenaline, and they are found within the CNS, PNS, and adrenal glands.

Outline
(1) Catecholamine synthesis, release, and inactivation.
(2) Organization and function of the dopaminergic system.
(3) Organization and function of the noradrenergic system.

Part I. Catecholamine synthesis, release, and inactivation

1. Tyrosine hydroxylase catalyzes the rate-limiting step in catecholamine synthesis

1.1 The amino acid, tyrosine -> DOPA -> Dopamine -> Norepinephrine (Figure 5.2).
1.2 Tyrosine is obtained from dietary protein and is transported from the blood into the brain.
1.3 Each step in the formation of catecholamines depends on a specific enzyme that acts as a catalyst (an agent that increases the rate of a chemical reaction) for that step.
1.4 Tyrosine hydroxylase is the rate-limiting enzyme in the pathway because it determines the overall rate of dopamine and norepinephrine formation.
Part I. Catecholamine synthesis, release, and inactivation

1. Tyrosine hydroxylase catalyzes the rate-limiting step in catecholamine synthesis

1.5 (1) The level of catecholamines within the nerve terminal, e.g., high catecholamine levels within the nerve terminal tend to inhibit tyrosine hydroxylase, serving as a negative feedback mechanism.

(2) The rate of cell firing, e.g., when neurons are activated and firing at a high rate, such as during stress, tyrosine hydroxylase would be stimulated.

These elegant mechanisms enable dopaminergic and noradrenergic neurons to carefully control their rate of neurotransmitter formation.

Part I. Catecholamine synthesis, release, and inactivation

1. Tyrosine hydroxylase catalyzes the rate-limiting step in catecholamine synthesis

1.6 Catecholamine formation can be increased by the administration of a biochemical precursor (i.e., to be converted into a particular neurotransmitter) such as L-DOPA (for the treatment of Parkinson’s disease).

1.7 Catecholamine formation can be decreased by the drug, AMPT (α-methyl-para-tyrosine). This compound blocks tyrosine hydroxylase, thus preventing overall catecholamine synthesis and causing a general depletion of DA and NE neurotransmitters.

1.8 AMPT treatment caused a return of depressive symptoms in patients who had previously recovered following treatment with antidepressants that act selectively on the noradrenergic system, indicating that the depressed patients’ recovery depends on the maintenance of adequate catecholamine levels in the brain.
2. Catecholamines are stored in and released from synaptic vesicles

2.1 Once catecholamines have been synthesized, they are transported into synaptic vesicles for later release (Figure 5.3).

2.2 Catecholaminergic neurons use a vesicular monoamine transporter (VMAT) to transport neurotransmitter molecules from the cytoplasm of the cell to the interior of the synaptic vesicles (Figure 5.3).

Vesicular packaging is important because (1) it provides a means for releasing a predetermined amount neurotransmitter (~several thousand molecules per vesicle), and (2) it protects the neurotransmitter from degradation by enzymes within the nerve terminal.
2. Catecholamines are stored in and released from synaptic vesicles

2.3 These VMAT proteins can be blocked/damaged by reserpine, causing low levels of DA and NE due to lack of protection of DA and NE from metabolizing enzymes located outside of the vesicles.

2.4 Behavioral effects of reserpine are sedation in animals and depressive symptoms in humans, and these effects can be reversed by restoration of catecholamines with DOPA, an immediate biochemical precursor of dopamine (Figure 5.4).

2.5 Release of catecholamines normally occurs [[when a nerve impulse enters the terminal and triggers one or more vesicles to release their contents into the synaptic cleft]] (Figure 5.5).

2.6 Psychostimulants, such as amphetamine and methamphetamine, can cause a release of catecholamines independently of nerve cell firing.

Catecholamine depletion: sedation and depressive symptoms

Catecholamine release: behavioral activation
2. Catecholamines are stored in and released from synaptic vesicles

2.7 In rodents, i.e., rats and mice, amphetamine increases locomotor activity. At high doses, locomotor activation is replaced by stereotyped behaviors including intense sniffing, repetitive head and limb movements, and licking & biting.

In humans, amphetamine causes increased alertness, heightened energy, euphoria, insomnia, and other behavioral effects.

2.8 Catecholamine release is inhibited by autoreceptors located on the cell bodies, terminals, and dendrites of dopaminergic and noradrenergic neurons by reducing the rate of firing of the cell (Figure 5.5).

2.9 Autoreceptor antagonists tend to enhance the rate of release by preventing the normal inhibitory effect of the autoreceptors.

2. Catecholamines are stored in and released from synaptic vesicles

Using NE α2-autoreceptor system as an example:

2.10.1 Physical withdrawal from opioid drugs such as morphine activates the noradrenergic system, which partially contributes to withdrawal symptoms, such as increased heart rate, elevated blood pressure, and diarrhea.

2.10.2 α2-agonists such as clonidine are used to treat opioid withdrawal due to their ability to stimulate the α2-autoreceptors and inhibit NE cell firing.

2.10.3 α2-antagonists such as yohimbine, which block the α2-autoreceptors and increase the NE cell firing and release, can provoke withdrawal symptoms in opioid-dependent patients (Figure 5.6).
3. Catecholamine inactivation occurs through a combination of reuptake and metabolism

3.1 Reuptake by transporters: After the neurotransmitter molecules are returned to the terminal through transporters, some of them are re-packaged into the vesicles for re-release while the remainder are broken down and eliminated (Figure 5.5).

3.2 Since the transporters are necessary for the rapid removal of catecholamines from the synaptic cleft, transporter-blocking drugs enhance the synaptic transmission of DA or NE by increasing the amount of neurotransmitter in the synaptic cleft.

3.2.1 Tricyclic antidepressants: to inhibit the reuptake of both NE and serotonin (5-HT) (i.e., reuptake blocker OR reuptake inhibitor).
3.2.2 Cocaine: to inhibit the reuptake of DA, NE, and 5-HT.

3.3 Metabolic breakdown: There are two enzymes mainly involved in the breakdown of catecholamines, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).

3.4 In humans, dopamine has only one major metabolite, homovanillic acid (HVA). Norepinephrine has two major metabolites, 3-methoxy-4-hydroxy-phenylglycol (MHPG) and vanillylmandelic acid (VMA).

3.5 Measurement of these metabolites in various fluid compartments (i.e., blood, urine, and cerebrospinal fluid) facilitate in determining the possible involvement of these neurotransmitters in mental disorders such as schizophrenia and depression.

3.6 MAO inhibitors: the treatment of depression.

3.7 COMT inhibitors: as a supplemental therapy to enhance the effectiveness of L-DOPA in treating Parkinson’s disease.
Part I. Catecholamine synthesis, release, and inactivation
Section Summary

1. The major catecholamine transmitters in the brain are dopamine (DA) and norepinephrine (NE).

**Synthesis**
2. The first, and also rate-limiting, step in this biochemical pathway is catalyzed by the enzyme, tyrosine hydroxylase (TH).

**Release**
3. The process of release is controlled by inhibitory autoreceptors located on the cell body, dendrites, and terminals of catecholamine neurons.

**Inactivation**
4. Catecholamines are inactivated by both transporters’ reuptake from the synaptic cleft and enzymatic degradation. MAO and COMT are two enzymes important in catecholamine metabolism.

**The Pharmacological Basis of Therapeutics**

KO: Drugs can modify catecholaminergic function by acting on the processes of synthesis, release, reuptake, or metabolism, to clinically treat various disorders or to experimentally study the functions of DA and NE.

3.14 Summary of the mechanisms by which drugs can alter synaptic transmission
Part II. Organization and function of the dopaminergic system

1. Two important dopaminergic cell groups are found in the midbrain

1.1 Several dense clusters of dopaminergic neuronal cell bodies are located near the base of the mesencephalon (midbrain): two important groups are A9 cell group (substantia nigra) and A10 group (ventral tegmental area, VTA). (Figure 5.7A).

1.2.1 The nigrostriatal tract: Axons of dopaminergic neurons in the substantia nigra ascend to a forebrain structure known as the caudate putamen or striatum.

1.2.2 This tract is severely damaged in Parkinson’s disease. Because the most prominent symptoms of Parkinson’s disease reflect deficits in motor function, such as tremors, postural disturbance, and difficulty in initiating voluntary movements, it is clear that this DA tract plays a crucial role in the control of movement.
1. Two important dopaminergic cell groups are found in the midbrain

1.3 The mesolimbic DA pathway: Axons of dopaminergic neurons in the VTA ascend to various structures of the limbic system including the nucleus accumbens, septum, amygdala, and hippocampus (Figure 5.7B).

1.4 The mesocortical DA pathway: Axons of dopaminergic neurons in the VTA ascend to the cerebral cortex, esp. the prefrontal area (Figure 5.7C).

1.5 The mesolimbic and mesocortical DA pathways are very important because they have been implicated in the neural mechanisms underlying drug abuse and schizophrenia.
1. Two important dopaminergic cell groups are found in the midbrain

1.6.1 6-OHDA (6-hydroxydopamine) is a neurotoxin which causes injury or death to DA nerve cells. Once 6-OHDA is administered into the brain, the DA nerve terminals are severely damaged and even the entire cell dies (Figure 5.8).

1.6.2 Animals with bilateral 6-OHDA lesions of DA pathways show severe behavioral dysfunction including sensory neglect, motivational deficits, and motor impairment. 

How important the DA neurotransmitter is for normal behavioral functioning!

Box 5.1. Parkinson’s Disease – A “Radical” Death of Dopaminergic Neurons?

B1. There is no doubt that progressive damage to the ascending dopaminergic system, esp. the nigrostriatal pathway, is largely responsible for the motor disturbance of Parkinson’s disease.

B1.1 Parkinsonian symptoms begin to appear once striatal DA levels decline by 70-80% from normal.

B1.2 There is a correlation between the degree of damage to the dopaminergic system and the severity of symptom manifestation.

B1.3 Destruction of the nigrostriatal DA pathway or blockade of striatal DA receptors in either animals or humans causes motor deficits resembling those seen in patients with Parkinson’s disease.

B1.4 Pharmacotherapies aiming at increasing DA availability or stimulating DA receptors reduce the behavioral symptoms.
Box 5.1. Parkinson’s Disease – A “Radical” Death of Dopaminergic Neurons?

B2.1 Unlike many of the classical drug treatment for psychiatric disorders that were discovered accidentally, L-DOPA treatment was conceived as a “rational therapy” for PD because its aim is to replace the DA lost due to degeneration of the nigrostriatal tract.

B2.2 There are many limitations of L-DOPA therapy, including a reduction in effectiveness over time, the development of dyskinesias (abnormal involuntary movements), and the occurrence of dopaminergic psychoses.

B3. The cause of PD remains enigmatic. PD is not inherited, i.e., genetics does not play a role in this disorder.

B4.1 Monkeys treated with MPTP (an DA neurotoxin) developed a behavioral syndrome very similar to PD that responded appropriately to L-DOPA.

B4.2 Biochemical and histological examination confirmed that their symptoms were due to a loss of DA neurons in the substantia nigra and a depletion of DA in the striatum.

Part II. Organization and function of the dopaminergic system

2. There are five main subtypes of dopamine receptors organized into D1- and D2-like families

2.1 Both D1- and D2-like receptors are found in large numbers in the striatum and the nucleus accumbens, which are major termination sites of the nigrostriatal and mesolimbic DA pathways, respectively.

2.2 D1- and D2-like receptors have opposite effects on the 2nd messenger substance, cyclic adenosine monophosphate (cAMP) (Figure 5.9).
Part II. Organization and function of the dopaminergic system

2. There are five main subtypes of dopamine receptors organized into D1- and D2-like families

2.3 D1-like (i.e., D1 and D5) receptors stimulate the enzyme adenyl cyclase, which is responsible for synthesizing cAMP. Subsequently, the rate of cAMP formation is increased.

2.4 D2-like (i.e., D2, D3, and D4) receptors inhibit adenyl cyclase, thereby decreasing the rate of cAMP synthesis.

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Part II. Organization and function of the dopaminergic system

3. Dopamine receptor agonists and antagonists affect locomotor activity and other behavioral functions

3.1 DA receptor agonists:

Apomorphine (activate both D1- and D2-like receptors)
1) At appropriate doses, apomorphine causes behavioral activation similar to that seen with classical stimulants amphetamine and cocaine.
2) It can also be used to treat erectile dysfunction in men.
3) Its therapeutic potential is limited by side effects, such as nausea.

SKF 38393 (activate D1 receptors)
1) Administration of this compound in rodents elicits self-grooming behavior.

Quinpirole (activate D2, D3, and D4 receptors)
1) Administration of this compound in rodents increases locomotion, yawning, and sniffing behavior.
3. Dopamine receptor agonists and antagonists affect locomotor activity and other behavioral functions

3.2 DA receptor antagonists:
3.2.1 The typical effect of administering a DA receptor antagonist is to verify the receptor mechanisms underlying specific behaviors. However, DA antagonists suppress spontaneous exploratory and locomotor behavior. At high doses, such drugs elicit a state known as catalepsy.

3.2.2 Catalepsy refers to a lack of spontaneous movement, which is demonstrated by showing that the subject does not change position when placed in an awkward, presumably uncomfortable posture (Figure 5.10).

3.2.3 Catalepsy is usually associated with D2 receptor blockers such as haloperidol, but it can also be elicited by giving a D1 receptor blocker such as SCH 23390.

3.2.4 Given the important role of the nigrostriatal DA pathway in movement, it is not surprising to learn that catalepsy is particularly related to the inhibition of DA receptors in the striatum.
3. Dopamine receptor agonists and antagonists affect locomotor activity and other behavioral functions

3.3 Behavioral supersensitivity to D2 receptors

3.3.1 When haloperidol (a D2 receptor antagonist) is given chronically to rats, the subjects develop a syndrome called behavioral supersensitivity, i.e., they respond more strongly (e.g., more locomotor activity) than control subjects (i.e., sham injections without haloperidol) when they are given a DA receptor agonist such as apomorphine.

3.3.2 A similar effect occurs following DA deplection by 6-OHDA.

3.3.3 Studies suggest that the supersensitivity associated with haloperidol and 6-OHDA treatment is related at least partly to an increase in the density of D2 receptors on the postsynaptic cells in the striatum, which is called receptor up-regulation, considered to be an adaptive response whereby the lack of normal DA neurotransmitter input causes the neurons to increase their sensitivity by making more receptors.

Box 5.2. Using “Gene Knockout” Animals to Study the Dopaminergic System

B1. Each gene knockout (KO) produces a unique behavioral phenotype (i.e., the behavior of the mutant strain compared to that of normal animals). For example, dopamine transporter KO mice are extremely hyperactive.
Box 5.2. Using “Gene Knockout” Animals to Study the Dopaminergic System

B2. Both DA transporter-KO and D1-KO mice show little or no increase in locomotion following psychostimulant treatment, indicating that the DA transporters on the presynaptic side and the D1 receptors on the postsynaptic side both play pivotal roles in the behavior-stimulating effects of cocaine and amphetamine.

B3. Mice lacking D1 or D3 receptors still show catalepsy following haloperidol treatment, whereas D2 KO mice are insensitive to the locomotor-inhibiting and cataleptic effects of haloperidol, clearly indicating that D2 receptors mediate the inhibitory effects of haloperidol on locomotor activity.

B4. Bottom line: The gene KO approach is an alternative to study the functions of specific receptors, but it only confirms part of theories developed from pharmacological studies.

Part II. Organization and function of the dopaminergic system

Section Summary

1. The neurons in the substantia nigra send their axons to the striatum, thus forming the nigrostriatal tract. This pathway plays an important role in the control of movement. It is severely damaged in the neurological disorder known as Parkinson’s disease.

2. The DA neurons in the VTA form two major DA pathways. One is the mesolimbic system, terminating in several limbic system structures, including the nucleus accumbens, amygdala, and hippocampus. The other is the mesocortical system, esp. terminating in the prefrontal cortex. Both DA pathways have been implicated in the mechanisms of drug abuse and schizophrenia.

3. D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors have opposite effects in modulating the 2nd messenger system. D1-like receptors: stimulate adenylyl cyclase -> increase $\uparrow$ cAMP synthesis D2-like receptors: inhibit adenylyl cyclase -> decrease $\downarrow$ cAMP synthesis
Part II. Organization and function of the dopaminergic system

Section Summary

4. In general, enhancement of dopaminergic function has an activating effect on behavior, whereas interference with DA causes a suppression of normal behaviors ranging from temporary sedation and catalepsy to the profound deficits observed following 6-OHDA treatment.

5. When D2 receptor transmission is persistently impaired either by chronic antagonist administration or by denervation (e.g., 6-OHDA lesions), animals become supersensitive to treatment with a D2 receptor agonist. This response is mediated at least partially by an up-regulation of D2 receptors by postsynaptic neurons in areas such as the striatum.

<table>
<thead>
<tr>
<th>TABLE 5.1 Drugs That Affect the Dopaminergic System</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>DOPA</td>
</tr>
<tr>
<td>Phenelzine</td>
</tr>
<tr>
<td>6-Methyl-para-tyrosine</td>
</tr>
<tr>
<td>(AMPT)</td>
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<tr>
<td>Reserpine</td>
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<tr>
<td>6-Hydroxydopamine (6-OHDA)</td>
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<td>Amphetamine</td>
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<tr>
<td>Cocaine and methylphenidate</td>
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<tr>
<td>Apomorphine</td>
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<td>SKF 38393</td>
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<td>Quinpirole</td>
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<tr>
<td>SCH 23390</td>
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<td>Haloperidol</td>
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Summary of the mechanisms by which drugs can alter synaptic transmission

Part III. Organization and function of the noradrenergic system
1. The ascending noradrenergic system originates in the locus coeruleus
   1.1 Axons of noradrenergic neurons in the locus coeruleus (LC) ascend to almost all areas of the forebrain, thus providing nearly all of the NE in the cortex, limbic system, thalamus, and hypothalamus. The LC also provides NE input to the cerebellum and the spinal cord (Figure 5.11).

   1.2 Norepinephrine also plays an important role in the peripheral nervous system.
1. The ascending noradrenergic system originates in the locus coeruleus

1.3 NE neurons in the LC showed a low rate of firing when rats were asleep. In contrast, presentation of novel sensory stimuli to the animals led to increased LC cell firing. These findings suggest that the noradrenergic neurons of the LC play an important role in vigilance (i.e., being alert to important stimuli in the environment) (Figure 5.12).

2. The cellular effects of norepinephrine and epinephrine are mediated by $\alpha$- and $\beta$-adrenergic receptors

2.1 Postsynaptic adrenoceptors are found at high densities in many brain areas, including the cerebral cortex, thalamus, hypothalamus, cerebellum, and various limbic system structures such as the hippocampus and amygdala.

2.2 $\alpha_2$-autoreceptors are located on noradrenergic nerve terminals and on the cell bodies of NE neurons in the LC. These autoreceptors cause an inhibition of noradrenergic cell firing and a reduction in NE release from the terminals.

2.3 $\beta_1$- and $\beta_2$-adrenoceptors (like D1 receptors) stimulate adenylyl cyclase and enhance the formation of cAMP.

2.4 $\alpha_2$-adrenoceptors (like D2 receptors) inhibit adenylyl cyclase and reduce the formation of cAMP.

2.5 $\alpha_1$-adrenoceptors operate through the phosphoinositide second-messenger system, which leads to an increased calcium (Ca$^{2+}$) within the postsynaptic cell.
3. Adrenergic agonists can stimulate arousal and eating behavior

3.1 NE is involved in many behavioral functions, including hunger and eating behavior, sexual behavior, fear and anxiety, and sleep and arousal.

3.2 Rats showed increased time awake after administration of small amount of either an $\alpha_1$-adrenergic agonist (phenylephrine) or a $\beta$-adrenergic agonist (isoproterenol) directly into the medial septum (Figure 5.13).

![Graph showing time awake after administration of different substances](image1)

3.3 When NE is injected in small amount directly into the PVN (paraventricular nucleus) of awake rats, it elicits a robust eating response even if the animals were not previously food-deprived (Figure 5.14). This effect is mediated by $\alpha_2$-receptors located within the PVN, because the response is blocked by an $\alpha_2$-receptor antagonist and is mimicked when an $\alpha_2$-agonist clonidine is injected into the PVN.

![Diagram showing NE injection into PVN and eating response](image2)
Part III. Organization and function of the noradrenergic system

4. A number of medications work by stimulating or inhibiting peripheral adrenergic receptors

4.1 Adrenergic agonists and antagonists are frequently used in the treatment of nonpsychiatric medical conditions. This is because of the widespread distribution and important functional role of adrenergic receptors in various peripheral organs (Table 5.2).

4.2 Albuterol ($\beta_2$-agonist): $\beta_2$-receptors are found in the airways, in contrast to the heart, which contains mainly $\beta_1$-receptors. Thus, albuterol is effective in alleviating the bronchial asthma (i.e., relaxation of smooth muscle of bronchi) without producing undesirable cardiovascular side effects.

4.3 Phenylephrine ($\alpha_1$-agonist): It is used as a nasal spray to constrict the blood vessels and reduce inflamed and swollen nasal membranes resulting from colds and allergies.

<table>
<thead>
<tr>
<th>Location</th>
<th>Action</th>
<th>Receptor subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Increased rate and force of contraction</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Constriction</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Smooth muscle of the trachea and bronchi</td>
<td>Relaxation</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Uterine smooth muscle</td>
<td>Contraction</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Bladder</td>
<td>Contraction</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Spleen</td>
<td>Contraction</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Iris</td>
<td>Pupil dilation</td>
<td>$\alpha$</td>
</tr>
<tr>
<td>Adipose (fat) tissue</td>
<td>Increased fat breakdown and release</td>
<td>$\beta$</td>
</tr>
</tbody>
</table>
Part III. Organization and function of the noradrenergic system

4. A number of medications work by stimulating or inhibiting peripheral adrenergic receptors

4.4 The $\alpha_1$-antagonist prazosin and the general $\beta$-adrenoceptor antagonist propranolol are both used in the treatment of hypertension.

4.5 Prazosin causes a dilation of blood vessels by blocking the $\alpha_1$-receptors responsible for constricting these vessels. In contrast, the main function of propranolol is to block the $\beta$-receptors in the heart, thereby reducing the heart’s contractile force.

4.6 Propranolol and other $\beta$-antagonists have also been applied to the treatment of generalized anxiety disorder.

$\beta$-blockers do not alleviate anxiety per se, but instead they may help the patient feel better by reducing some of distressing physical symptoms of the disorder.

Part III. Organization and function of the noradrenergic system

Section Summary

1. The most important cluster of noradrenergic neurons is located in the locus coeruleus. These neurons innervate almost all areas of the forebrain.

2. The cells in the LC are relatively inactive during sleep, but they fire at a rapid rate in response to novel sensory stimuli, indicating that the NE system is important in the maintenance of vigilance.

3. Both $\beta$-receptor subtypes enhance the synthesis of cAMP, while $\alpha_2$-receptors inhibit cAMP formation.

4. The $\alpha_1$-antagonist prazosin and the general $\beta$-receptor antagonist propranolol are used in the treatment of hypertension. $\beta$-antagonists are used in treating generalized anxiety disorders, because they reduce some of somatic symptoms associated with anxiety.

5. In general, the clinical application of adrenoceptor agonists and antagonists can be understood from the receptor subtypes in specific tissues and the resulting physiological effect of stimulating or blocking these receptors.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>Phenelzine</td>
<td>Increases catecholamine levels by inhibiting MAO</td>
</tr>
<tr>
<td>α-Methyl-para-tyrosine (AMPT)</td>
<td>Depletes catecholamines by inhibiting tyrosine</td>
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<tr>
<td></td>
<td>hydroxylase</td>
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<tr>
<td>Reserpine</td>
<td>Depletes catecholamines by inhibiting vesicular</td>
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<tr>
<td></td>
<td>uptake</td>
</tr>
<tr>
<td>6-Hydroxydopamine (6-OHDA)</td>
<td>Damages or destroys catecholaminergic neurons</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Releases catecholamines</td>
</tr>
<tr>
<td>Cocaine and methylphenidate</td>
<td>Inhibits catecholamine reuptake</td>
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<tr>
<td>Desipramine</td>
<td>Selectively inhibits NE reuptake</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Stimulates α₁-receptors (agonist)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Stimulates α₂-receptors (agonist)</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Stimulates β-receptors (partially selective for β₂)</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Blocks α₁-receptors (antagonist)</td>
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<tr>
<td>Yohimbine</td>
<td>Blocks α₂-receptors (antagonist)</td>
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<tr>
<td>Propranolol</td>
<td>Blocks β-receptors generally (antagonist)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Blocks β₁-receptors (antagonist)</td>
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