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SYMPATHOMIMETIC AND SYMPATHOLYTIC AGENTS: MULTIFUNCTIONAL ESSENTIAL DRUGS

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ABSTRACT

Sympathomimetics are drugs that mimic the stimulation of the sympathetic nervous system. They are classified as directly acting (act directly on α or β receptors), indirectly acting (act by providing more norepinephrine to act on α or β receptors), or mixed acting (act by both mechanisms). These drugs are used clinically to treat glaucoma, anaphylactic shock, chronic obstructive pulmonary disease, hypotension, hypertension, heart failure, nasal congestion, premature labour, attention-deficit/hyperactivity disorder, narcolepsy, and acute or chronic asthma. The α or β adrenergic antagonists block or attenuate the effect of sympathomimetics on α or β receptors. Alpha blockers are used clinically to treat hypertension and benign prostatic hyperplasia. Beta blockers are used clinically to treat ischemic heart disease, essential hypertension, cardiac arrhythmias, congestive heart failure, glaucoma, hyperthyroidism, and surgical removal of pheochromocytoma, nonparkinsonian tremor, migraine headache (prophylaxis), and a wide variety of anxiety situations. A sympatholytic (or sympathoplegic) drug is a medication that opposes the downstream effects of postganglionic nerve firing in effector organs innervated by the sympathetic nervous system (SNS). They are indicated for various functions; for example, they may be used as antihypertensives. They are also used to treat anxiety, such as generalized anxiety disorder, panic disorder and PTSD. In some cases, such as with Guanfacine, they have also shown to be beneficial in the treatment of ADHD.

KEYWORDS: Sympathomimetic, Sympatholytic, Alpha Blocker, Beta Blocker, CNS, ANS.

INTRODUCTION

Sympathomimetic drugs are used to treat cardiac arrest and low blood pressure, or even delay premature labor, among other things. These drugs can act through several mechanisms, such as directly activating postsynaptic receptors, blocking breakdown and reuptake of certain neurotransmitters, or stimulating production and release of catecholamines. α Adrenergic receptor antagonists; α Adrenergic receptors; β Adrenergic receptor antagonists; β Adrenergic receptors; Catecholamines; Sympathomimetics.[1]

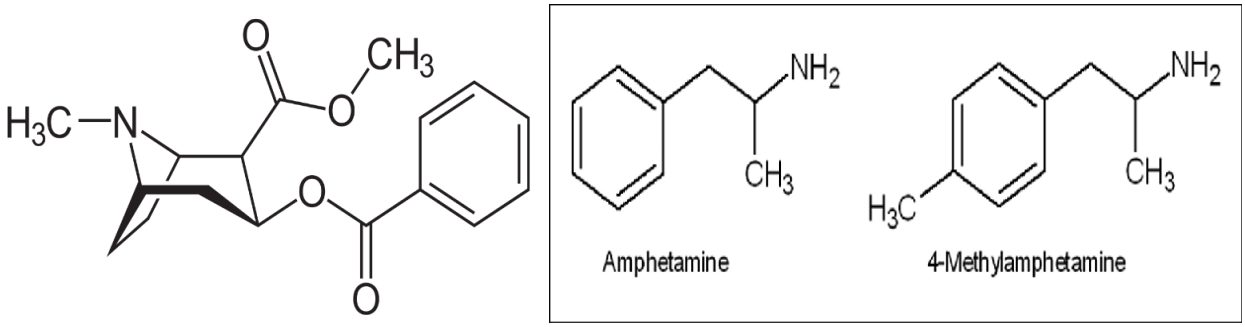

Figure-1: Structure of somr Sympathomimetic Agents- Cocaine and Amphetamine.

Sympathomimetic drugs—such as cocaine, amphetamines, phencyclidine hydrochloride (PCP), and lysergic acid diethylamide (LSD)—can precipitate a hypertensive emergency. Cocaine hypertensive emergencies have been documented in patients with illicit use and patients suffering from iatrogenic complications due to epistaxis treatment or when cocaine is used as a topical anesthetic for laryngoscopy. Cocaine

blocks the presynaptic reuptake of norepinephrine and dopamine, releases norepinephrine from sympathetic nerve terminals, and stimulates adrenal gland catecholamine release. Patients present with agitation, tachycardia, hypertension, mydriasis, and hyperthermia. Other agents that can precipitate a hypertensive emergency include dietary supplements such as Ephedra sinica, also known as ma-huang. This supplement contains ephedrine, a chemical that stimulates the nervous and endocrine systems to generate an acute rise in BP and has been temporally associated with stroke, MI, and sudden death. Although banned by the U.S. Food and Drug Association in 2006, it can still be obtained outside the United States and via Internet sources. Patients receiving monoamine oxidase inhibitor therapy who consume tyramine-containing foods may develop a hyperadrenergic state and resultant hypertensive crisis. Patients present with tachycardia, elevated BP, diaphoresis, chest pain, and—depending on the agent—mental status changes. Licorice can also cause acute elevations in BP and complications may include PRES. The active agent, glycyrrhic acid, inhibits 11β-hydroxysteroid dehydrogenase, causing mineralocorticoid excess. Most commercial preparations do not have enough of this compound to cause adverse effects, but some "original" or "old time" formulations may and, if consumed in large amounts, can lead to hypertensive crisis.

Patients with monoamine oxidase inhibitor toxicity often benefit from intravenous benzodiazepine. Phentolamine, nitroglycerin, and calcium channel blockers may also be used. These patients should be closely monitored, as the hypertensive phase is often followed by a hypotensive phase.

Pharmacology of Sympathomimetic Drug

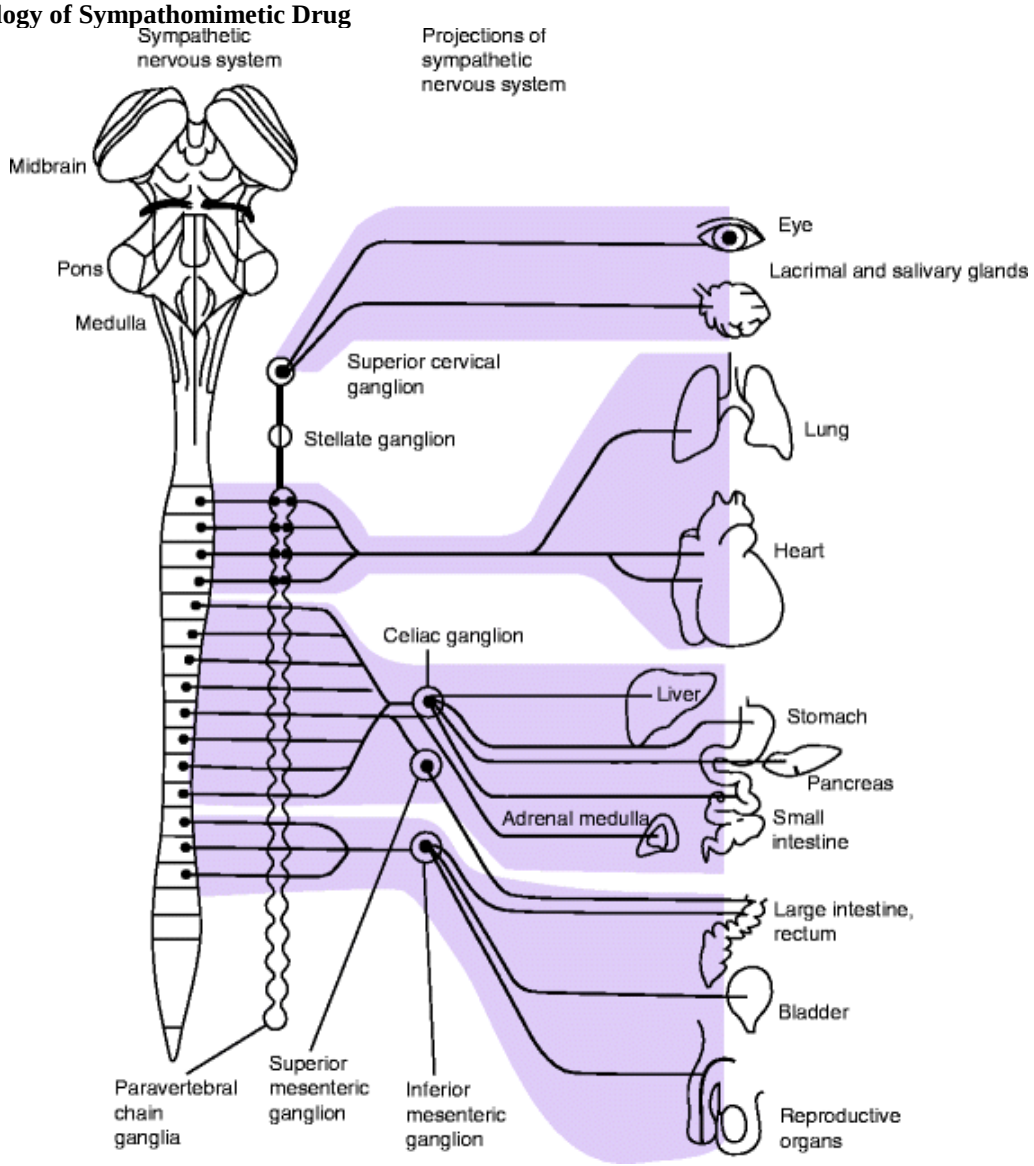

Figure-2: Pharmacology of Sympathomimetic Drugs.

The sympathomimetic drugs are grouped together because they can increase blood pressure and, in part, act like norepinephrine (NE). Drugs in this group work by a variety of mechanisms, including the release of NE from synaptic granules (benzphetamine, phendimetrazine, phentermine, and diethylpropion); the blockade of NE reuptake (mazindol); or the blockade of reuptake of both NE and serotonin (5-hydroxytryptomine, 5-HT; i.e., sibutramine). All of these drugs are absorbed orally and reach peak blood concentrations within a short time. The half-life in blood is also short for all except the two pharmacologically active metabolites of sibutramine, which have a long half-life.2 Although the two metabolites of sibutramine are active, this is not true for the metabolites of other drugs in this group. Liver metabolism inactivates a large fraction of these drugs before excretion. Side effects include dry mouth, constipation, and insomnia. Food intake is suppressed either by delaying the onset of a meal or by producing early satiety. Sibutramine and mazindol have both been shown to increase thermogenesis as well.[2]

Mechanism of Action

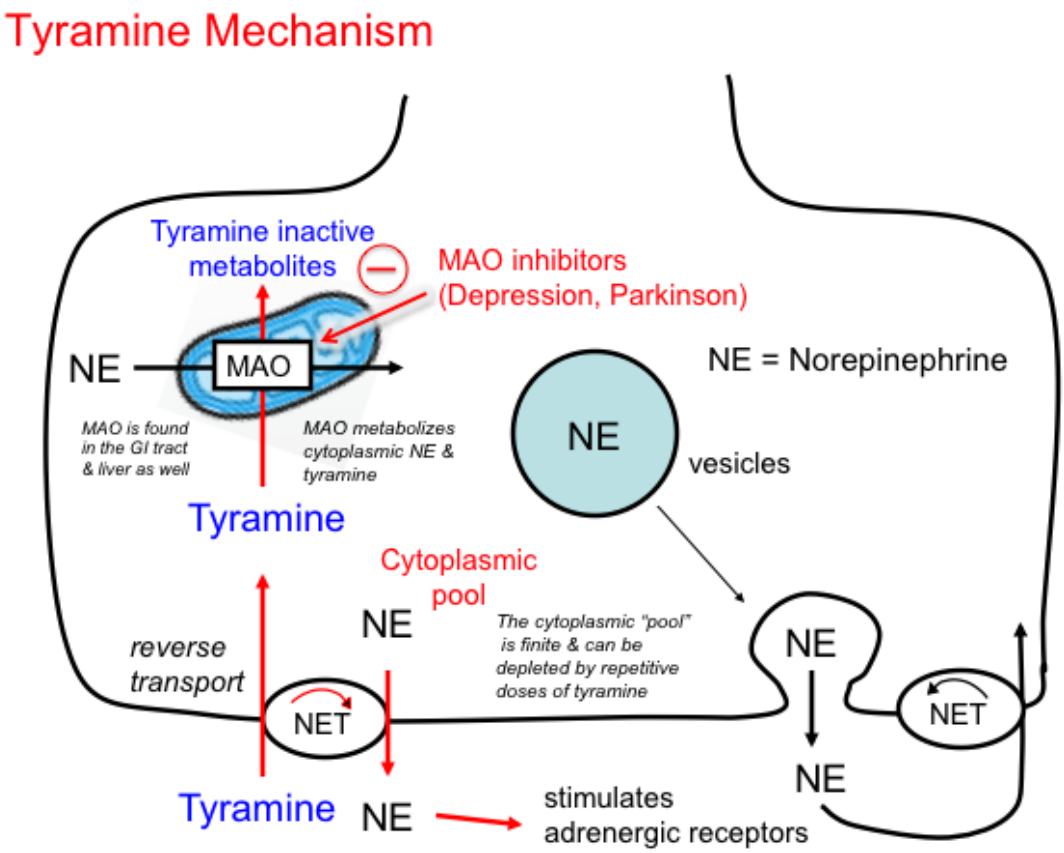

Figure-3: Mechanism of Action of Sympathomimetic Drug.

The mechanisms of sympathomimetic drugs can be direct-acting (direct interaction between drug and receptor), such as α-adrenergic agonists, β-adrenergic agonists, and dopaminergic agonists; or indirect-acting (interaction not between drug and receptor), such as MAOIs, COMT inhibitors, release stimulants, and reuptake inhibitors that increase the levels of endogenous catecholamines.

SAR of Sympathomimetic Agents

For maximum sympathomimetic activity, a drug must have:

1. Amine group two carbons away from an aromatic group
2. A hydroxyl group at the chiral beta position in the R-configuration
3. Hydroxyl groups in the meta and para position of the aromatic ring to form a catechol which is essential for receptor binding

The structure can be modified to alter binding. If the amine is primary or secondary, it will have direct action, but if the amine is tertiary, it will have poor direct action. Also, if the amine has bulky substituents, then it will have greater beta adrenergic receptor activity, but if the substituent is not bulky, then it will favor the alpha adrenergic receptors. A primary or secondary aliphatic amine separated by 2 carbons from a substituted benzene ring is minimally required for high agonist activity. The pKa of the amine is approximately the presence of hydroxyl group in the benzene ring at 3rd and 4th position shows maximum alpha- and beta-adrenergic activity.[3]

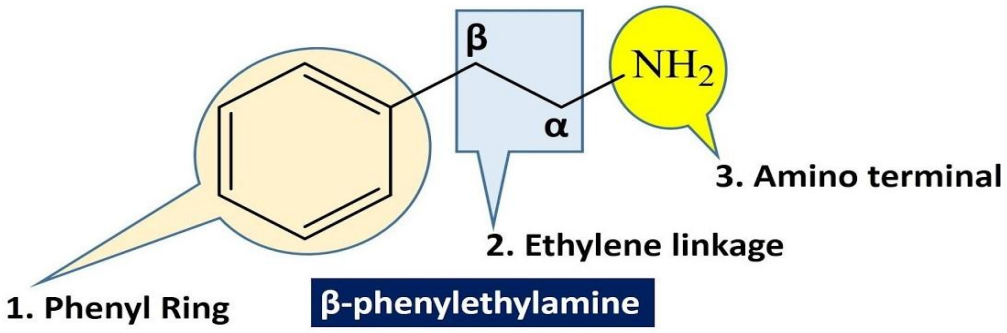

Figure-4: SAR of Sympathomimetic Agents.

Classification of Sympathomimetic Agents

Direct-acting

Adrenergic receptor agonists: Direct stimulation of the α- and β-adrenergic receptors can produce sympathomimetic effects. Salbutamol is a widely used direct-acting β_2-agonist. Other examples include phenylephrine, isoproterenol, and dobutamine.

Dopaminergic agonists: Stimulation of the D1 receptor by dopaminergic agonists such as fenoldopam is used intravenously to treat hypertensive crisis.

Indirect-acting: Dopaminergic stimulants such as amphetamine, ephedrine, and propylhexedrine work by causing the release of dopamine and norepinephrine, along with (in some cases) blocking the reuptake of these neurotransmitters.

Indirect Acting

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Cross-reactivity

Illegal drugs such as cocaine and MDMA also affect dopamine, serotonin, and norepinephrine. Norepinephrine is synthesized by the body from the amino acid tyrosine, and is used in the synthesis of epinephrine, which is a stimulating neurotransmitter of the central nervous system. Thus, all sympathomimetic amines fall into the larger group of stimulants (see psychoactive drug chart). In addition to intended therapeutic use, many of these stimulants have abuse potential, can induce tolerance, and possibly physical dependence, although not by the same mechanism(s) as opioids or sedatives. The symptoms of physical withdrawal from stimulants can include fatigue, dysphonic mood, increased appetite, vivid or lucid dreams, hypersomnia or insomnia, increased movement or decreased movement, anxiety, and drug craving, as is apparent in the rebound withdrawal from certain substituted amphetamines. Physical withdrawal from some sedatives can be potentially lethal, for instance benzodiazepine withdrawal syndrome. Opioid withdrawal is very uncomfortable, often described as a bad case of the flu, with possibly severe abdominal cramps and diarrhoea as central symptoms, but it is rarely lethal unless the user has a comorbid condition. Sympathomimetic drugs are sometimes involved in development of cerebral vasculitis and generalized polyarteritis nodosa like diseases involving immune-complex deposition. Known reports of such hypersensitivity reactions include the use of pseudoephedrine, phenylpropanlolamine, methamphetamine and other drugs at prescribed doses as well as at over-doses.

Sympatholytic Agents

A sympatholytic is a medication which inhibits the functioning of the sympathetic nervous system (SNS). They are used as antihypertensives. They mainly comprise antiadrenergic agents, but also anticholinergics in the case of the nicotinic antagonist, since nicotinic receptors relay the signals of the SNS across the ganglia.[4]

Mechanism of Action

Antiadrenergic agents inhibit the signals of epinephrine and norepinephrine. They are primarily postsynaptic adrenergic receptor antagonists (alpha and beta adrenergic receptor antagonists, or "blockers"), inhibiting the downstream cellular signaling pathways of adrenergic receptors. However, there are exceptions: clonidine is an adrenergic agonist at the α2 receptor; since this receptor is located presynaptically, agonism at this receptor inhibits the presynaptic release of adrenaline and noradrenaline, preventing postsynaptic adrenergic receptor activation and downstream signaling. Another way to inhibit adrenergic receptor signaling is by blocking the synthesis of catecholamines. Methyltyrosine, for example, inhibits one of the key enzymes in the pathway: tyrosine hydroxylase. For neurotransmitters to be released, they first must be stored in synaptic vesicles. Reserpine works by inhibiting VMAT, preventing the storage of neurotransmitters into synaptic vesicles. If VMAT is inhibited, neurotransmitters won't be released into the synaptic cleft, thereby inhibiting their downstream effect. Other drugs are preferentially toxic to sympathetic neurons. One method of obtaining such specificity is to exploit

drugs that are substrates for a transporter preferentially expressed on sympathetic terminals, such as the norepinephrine transporter. Such transports allows the drugs to accumulate within sympathetic neurones, where they can act to inhibit sympathetic function. Such drugs include bretylium, guanethidine and 6-hydroxydopamine.[5]

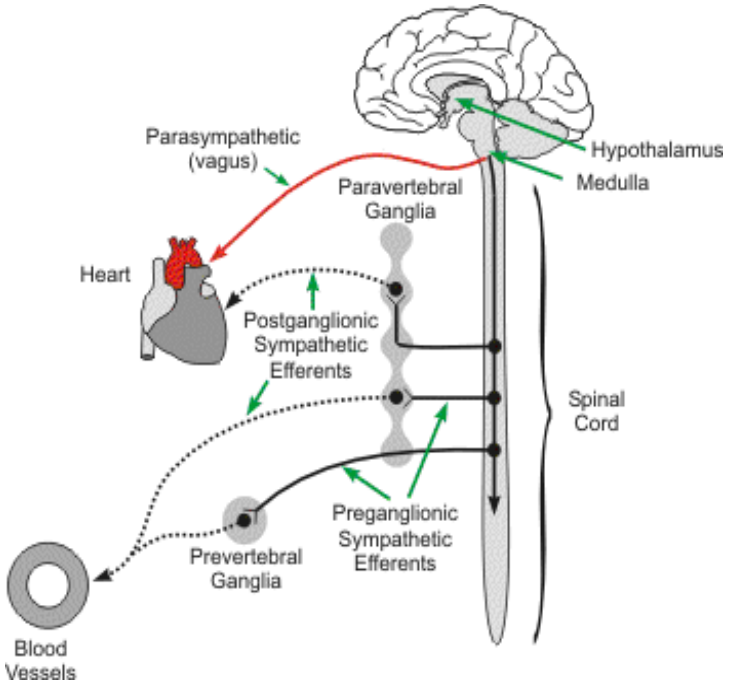

Figure-5: Mechanism of Action of Sympatholytic Agents.

Classification

Sympatholytic drugs include several different types of drugs, butall reduce blood pressure by inhibiting or blocking the sympathet-ic nervous system. They're classified by their site or mechanism of action and include: central-acting sympathetic nervous system inhibitors (clonidine and methyldopa)

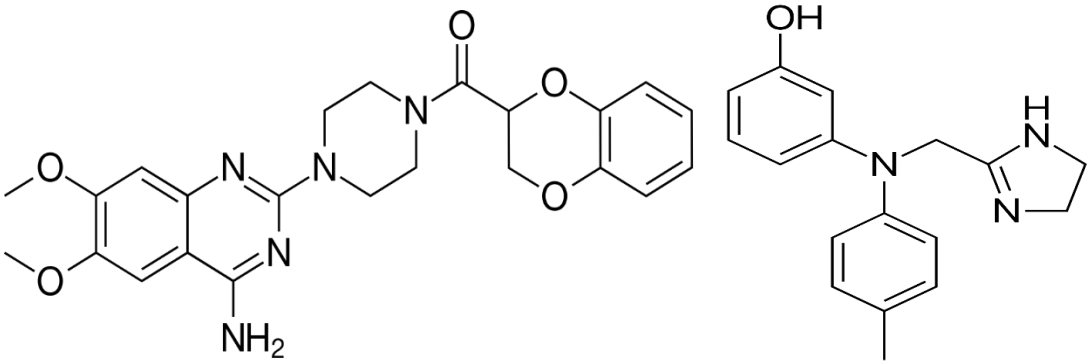

Figure-6: Structure of Doxazosin And Phentolamine.

Alpha-adrenergic blockers (doxazosin, phentolamine, prazosin, and terazosin)

Mixed alpha- and beta-adrenergic blockers (carvedilol and la-betalol)

Norepinephrine depletors (guanadrel, guanethidine, and reser-pine—these are rarely used).

Pharmacokinetics

Most sympatholytic drugs are absorbed well from the GI tract, dis-tribute widely, metabolized in the liver, and excreted primarily in urine.

Pharmacodynamics

All sympatholytic drugs inhibit stimulation of the sympathetic nervous system, causing dilation of the peripheral blood vessels or decreased cardiac output, thereby reducing blood pressure.[6]

Pharmacotherapeutics

If blood pressure fails to come under control with beta-adrenergic blockers and diuretics, an alpha-adrenergic blocker, such as prazosin, or a mixed alpha- and beta-adrenergic blocker, such as la-betalol, may be used. If the patient fails to achieve the desired blood pressure, the

physician may add a drug from a different class, substitute a drug in the same class, or increase the drug dosage.

Drug interactions

Sympatholytic drugs can create these drug interactions:
Carvedilol taken with antidiabetics may result in increased hypoglycaemic effect.
Carvedilol taken with calcium channel blockers may result in in-creased conduction disturbances.
Carvedilol taken with digoxin may result in increased digoxin levels.
Carvedilol taken with rifampin decreases carvedilol levels.
Clonidine plus tricyclic antidepressants may increase blood pressure.
Clonidine taken with CNS depressants may worsen CNS depression.
Reserpine taken with diuretics or other hypotensive agents can increase the hypotensive effects of reserpine.
Reserpine taken with cardiac glycosides can lead to cardiac arrthymias.

Anxiety Beta blockers

There is clear evidence from many controlled trials in the past 25 years that beta blockers are effective in anxiety disorders, though the mechanism of action is not known.

Some people have used beta blockers for performance type social anxiety, or "stage fright." In particular, musicians, public speakers, actors, and professional dancers, have been known to use beta blockers to avoid stage fright and tremor during public performance and especially auditions. The physiological symptoms of the fight/flight response associated with performance anxiety and panic (pounding heart, cold/clammy hands, increased respiration, sweating, etc.) are significantly reduced, thus enabling anxious individuals to concentrate on the task at hand. Stutterers also use beta blockers to avoid fight/flight responses, hence reducing the tendency to stutter.[7]

Since they promote a lower heart rate and reduce tremor, beta blockers have been used by some Olympic marksmen to enhance performance, though beta blockers are banned by the International Olympic Committee (IOC). Although they have no recognizable benefit to most sports, it is acknowledged that they are beneficial to sports such as archery and shooting. A recent, high-profile transgression took place in the 2008 Summer Olympics, where 50 meter pistol silver medalist and 10 meter air pistol bronze medalist Kim Jong-su tested positive for propranolol and was stripped of his medal.

Posttraumatic stress disorder (PTSD) is theorized to be the result of neurological patterns caused by adrenaline and fear in the brain. By administering beta blockers which can cross the blood brain barrier immediately following a traumatic event, as well as over the next couple weeks, the formation of PTSD has been reduced in clinical studies.[8]

Alpha2 adrenergic agonist

Alpha2 adrenergic agonist can also be used to treat anxiety and panic, such as Generalized Anxiety Disorder, Panic Disorder or PTSD. Alpha2-adrenergic receptor agonists, such as clonidine and guanfacine, act at noradrenergic autoreceptors to inhibit the firing of cells in the locus ceruleus, effectively reducing the release of brain norepinephrine. Clonidine has shown promise among patients with Anxiety, Panic and PTSD in clinical trials and was used to treat severely and chronically abused and neglected preschool children. It improved disturbed behavior by reducing aggression, impulsivity, emotional outbursts, and oppositionality. Insomnia and nightmares were also reported to be reduced.

Kinzie and Leung prescribed the combination of clonidine and imipramine to severely traumatized Cambodian refugees with Anxiety, Panic and PTSD. Global symptoms of PTSD were reduced among sixty-six percent and nightmares among seventy-seven percent. Guanfacine produces less sedation than clonidine and thus may be better tolerated. Guanfacine reduced the trauma-related nightmares.[9]

Alpha blockers

Prazosin is an α_1-blocker that acts as an inverse agonist at alpha-1 adrenergic receptors. Raskind and colleagues studied the efficacy of prazosin for PTSD among Vietnam combat veterans in a 20-week double-blind crossover protocol with a two-week drug washout to allow for return to baseline. The CAPS and the Clinical Global Impressions-Change scale (CGI-C) were the primary outcome measures. Patients who were taking prazosin had a robust improvement in overall sleep quality (effect size, 1.6) and recurrent distressing dreams (effect size, 1.9). In each of the PTSD symptom clusters the effect size was medium to large: 0.7 for reexperiencing or intrusion, and 0.6 for avoidance and numbing, and 0.9 for hyperarousal. The reduction in CGI-C scores (overall PTSD severity and function at endpoint) also reflected a large effect size (1.4). Prazosin appears to have promise as an effective treatment for PTSD-related sleep disturbance, including trauma-related nightmares, as well as overall anxiety and PTSD symptoms.[10]

CONCLUSION

Sympathomimetic drugs (also known as adrenergic drugs and adrenergic amines) are stimulant compounds which mimic the effects of endogenous agonists of the sympathetic nervous system. Examples of sympathomimetic effects include increases in heart rate, force of cardiac contraction, and blood pressure. The primary endogenous agonists of the sympathetic nervous system are the catecholamines (i.e., epinephrine [adrenaline], norepinephrine [noradrenaline], and

dopamine), which function as both neurotransmitters and hormones. Central sympatholytic drugs reduce blood pressure mainly by stimulating central α(2) -adrenergic receptors in the brainstem centers, thereby reducing sympathetic nerve activity and neuronal release of norepinephrine to the heart and peripheral circulation. • This class of drugs, however, is currently used mainly as fourth-line (or beyond) drug therapy for hypertension because of side effects of drowsiness, fatigue, and dry mouth. • Rebound hypertension is also another major concern in certain drugs with a short half-life, particularly in patients who are nonadherent to the regimen. Therefore, their use on a "PRN" basis for treatment of blood pressure surge in the absence of symptoms or acute target complications should also be avoided.

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