Adrenergic Storm And Cardiovascular System

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Defination : An **adrenergic storm** is a sudden and dramatic increase in serum levels of the catecholamines adrenalin and noradrenalin (also known as epinephrine and norepinephrine respectively), with a less significant increase in dopamine transmission. It is a life-threatening condition because of extreme tachycardia and hypertension, and is especially dire for those with prior heart problems. If treatment is prompt, prognosis is good; typically large amounts of diazepam or other benzodiazepines are administered alongside beta blockers. Beta blockers are contraindicated in some patients, so other anti-hypertensive medication such as clonidine may be used. It is usually caused by overdose of stimulants, especially cocaine, but can also arise from improper eating habits while taking monoamine oxidase inhibitors. A subarachnoid hemorrhage can also cause an adrenergic storm, and catecholamine storm is part of the normal course of Rabies infection, and is responsible for the severe feelings of agitation, terror, and dysautonomia present in the pre-coma stage of the disease (Elenkov,et al.,2000).

Adrenaline

Adrenaline is a prototypical sympathomimetic drug (used as a template against which other drugs are compared); this is because it acts on both alpha and beta receptors. It produces its effects through the second messenger system.

On alpha 1 receptors, it acts through IP3 second messenger system by increasing Ca++ levels.

On alpha 2 receptors, it acts by decreasing the cAMP levels.

On beta 1, 2 and 3 receptors it acts by causing an increase in the cAMP levels (Jones, et al., 1996).

Pharmacological Actions

Predominantly acts on:

- Blood Pressure
- Blood vessels
- Heart
- ECG

Blood Pressure:

Adrenaline acts on both alpha and beta receptors, thus the blood is redistributed.

Arterial Pressure = Cardiac Output x Total Peripheral Resistance

Cardiac Output = Heart rate x Stroke volume

Beta 1 receptors stimulate the heart and produce a positive ionotropic (increased force of contraction) and a positive chronotropic (increased heart rate) effect.

Vasodilatation occurs in the limbs while vasoconstriction occurs elsewhere, beta 1 receptors cause vasodilatation in the heart, alpha receptors are also stimulated, and thus an interplay between alpha and beta receptors occurs. At physiological concentrations, beta receptors are stimulated first. At higher concentrations alpha receptors are stimulated first. Thus the total peripheral resistance either remains the same, increases or decreases, depending on the type of receptors stimulated.

The action of drugs depends on:

Receptor type

Affinity of drugs for receptors

Intrinsic activity of drugs

Compensatory responses (e.g. reflex bradycardia)

Systolic blood pressure, under adrenaline influence, is increased. The diastolic pressure may not increase, decrease or increase very slightly. It mainly depends on the total peripheral resistance, in excessive vasodilatation it may even fall.

The net result is that the pulse pressure gets widened (Elenkov,et al.,2000).

Blood Vessels:

Blood vessels are constricted or dilated.

The skin, mucous membrane, kidney and pulmonary blood vessels constrict under the influence of adrenaline.

The skeletal muscle blood vessels are dilated.

Coronary blood flow increases due to:

Intrinsic activity, by the release of adenosine, which causes vasodilatation.

Beta 2 receptors may also be present.

Cerebral blood flow depends mostly on systolic pressure, but is auto regulated. It generally increases (Elenkov,et al.,2000).

Heart

Due to positive chronotropic and positive ionotropic effect, the work load on the heart increases, this increases the oxygen consumption. Apart from this the conduction velocity also increases (positive dromotropic effect). The effective refractory period decreases. The excitability of the heart increases (positive bathmotropic effect). In higher doses, arrhythmias may occur. Positive lusiotropic effect is also seen (increase in calcium uptake by cardiomyocytes leading to increased myocardial relaxation) (Elenkov,et al.,2000).

ECG:

Adrenaline may produce ST elevation or depression. It may also produce flattening or inversion of T wave especially in individuals prone to heart diseases (above 40 yrs etc.). Both these findings indicate ischemia.

The coronary blood flow increases but the oxygen consumption is much more. There is thus relative ischemia.

Central Nervous System:

Adrenaline is a catecholamine and does not cross the blood brain barrier. At higher concentration person becomes apprehensive, restless and anxiety is visible as well as the feeling of doom. This is because of somatic manifestation of anxiety (as tachycardia, tremors occur because of adrenaline due to synchronous and enhanced firing and increased metabolism) (Marik, el al., 2007)

Metabolic Effects:

1. Beta 3 receptors are present in the lipocytes and adipose tissue. Adrenaline acts to cause breakdown of triglycerides into free fatty acids and glycerol. Adrenaline stimulates the triglyceride lipase which causes this breakdown.
2. Increased glucose levels or hyperglycemia occurs due to :

Insulin secretion as a whole is decreased. In beta cells of pancreas beta receptors increase the secretion, while alpha 2 receptors cause a decrease. Alpha 2 effects predominate.

Decreased peripheral utilization

Increased glucagon secretion (beta effect)

Increased glycogenolysis (beta effect) in both liver and skeletal muscles.

Reduction in potassium levels in the blood, increasing reuptake by skeletal muscles. As more potassium is released, therefore, by virtue of

adrenaline more is transported back. There is a narrow range within which the potassium levels are maintained (3.5-5.5 mEq) (Moro, et al., 2013).

Adrenergic receptor

The adrenergic receptors (or adrenoceptors) are a class of G protein-coupled receptors that are targets of the catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline).

Many cells possess these receptors, and the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system. The sympathetic nervous system is responsible for the fight-or-flight response, which includes widening the pupils of the eye, mobilizing energy, and diverting blood flow from non-essential organs to skeletal muscle (Large, et al., 1997).

History

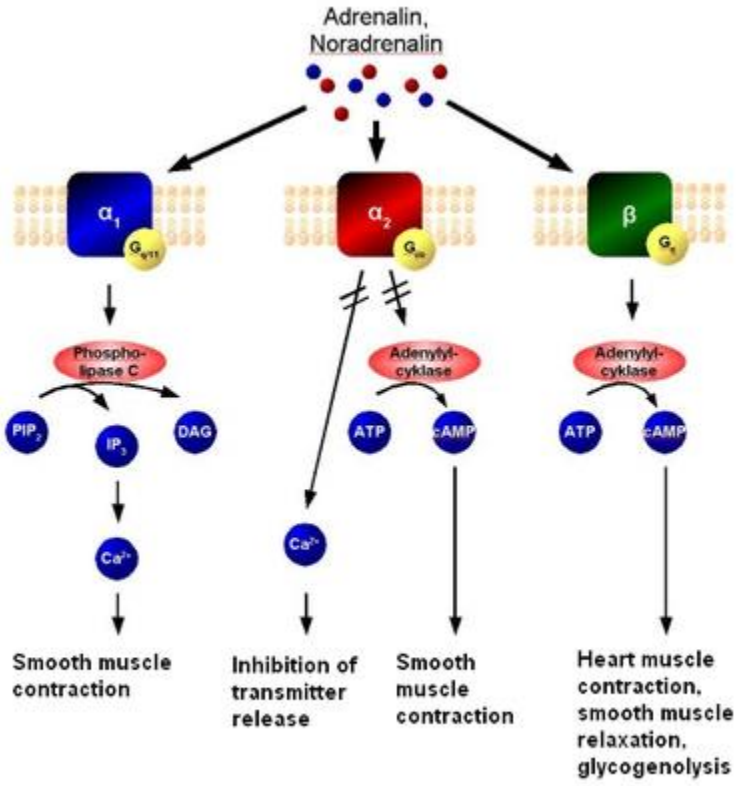
Raymond Ahlquist, Professor of Pharmacology at Medical College of Georgia, published a paper concerning adrenergic nervous transmission in 1948 but its significance was largely ignored at that time. However, in 1954 he was able to incorporate his findings in a textbook, Drill's Pharmacology in Medicine, and thereby firmly establish the essential role played by α and ß receptor sites in the adrenaline/nor-adrenaline cellular mechanism. His discovery would revolutionise advances in pharmacotherapeutic research, allowing the selective design of specific molecules to target medical ailments rather than rely upon traditional research into the efficacy of pre-existing herbal medicines (Mayersohn, et al., 1995).

Categories

There are two main groups of adrenergic receptors, α and ß, with several subtypes.

α receptors have the subtypes α1 (a Gq coupled receptor) and α2 (a Gi coupled receptor). Phenylephrine is a selective agonist of the α receptor.

ß receptors have the subtypes ß1, ß2 and ß3. All three are linked to Gs proteins (although ß2 also couples to Gi), which in turn are linked to adenylate cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA), which mediates some of the intracellular events following hormone binding. Isoprenaline is a non-selective agonist (Ahlquist, et al., 1984)



The mechanism of adrenergic receptors. Adrenaline or noradrenaline are receptor ligands to either α1, α2 or ß-adrenergic receptors. α1 couples to Gα, which results in increased intracellular Ca^{2+} and subsequent smooth muscle contraction. α2, on the other hand, couples to Gi, which causes a decrease of cAMP activity and a resulting smooth muscle relaxation. ß receptors couple to Gs, and increases intracellular cAMP activity, resulting in e.g. heart muscle contraction, smooth muscle relaxation and glycogenolysis (Sagrada, et al ., 1987).

Roles in circulation

Epinephrine (adrenaline) reacts with both α- and ß-adrenoreceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to epinephrine, when activated, they override the vasodilation mediated by ß-adrenoreceptors because there

are more peripheral α1 receptors than β-adrenoreceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. At lower levels of circulating epinephrine, β-adrenoreceptor stimulation dominates, producing vasodilation followed by decrease of peripheral vascular resistance (Elliott, et al., 1997).

Subtypes

α receptors

α receptors have several functions in common, but also individual effects. Common (or still unspecified) effects include:

Vasoconstriction of veins

Decrease motility of smooth muscle in gastrointestinal tract (Whalen, et al., 1992).

α_1 receptor

α1-adrenergic receptors are members of the Gq protein-coupled receptor superfamily. Upon activation, a heterotrimeric G protein, Gq, activates phospholipase C (PLC). The PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP2), which in turn causes an increase in inositol triphosphate (IP3) and diacylglycerol (DAG). The former interacts with calcium channels of endoplasmic and sarcoplasmic reticulum, thus changing the calcium content in a cell. This triggers all other effects.

Specific actions of the α1 receptor mainly involve smooth muscle contraction. It causes vasoconstriction in many blood vessels, including those of the skin, gastrointestinal system, kidney (renal artery) and brain(Nisoli, et al ., 1996).

Other areas of smooth muscle contraction are:

Ureter

Vas deferens

Hair (arrector pili muscles)

Uterus (when pregnant)

Urethral sphincter

Urothelium and lamina propria.

Bronchioles (although minor due to the relaxing effect of ß2 receptor on bronchioles)

Blood vessels of ciliary body (stimulation causes mydriasis)

Further effects include glycogenolysis and gluconeogenesis from adipose tissue and liver, as well as secretion from sweat glands and Na+ reabsorption from kidney.

Antagonists may be used primarily in hypertension, anxiety disorder, and panic attacks (Schmitz, et al., 1981).

α_2 receptor

The α2 receptor is a presynaptic receptor, causing negative feedback on, for example, norepinephrine. When NA is released into the synapse, it feeds back on the α2 receptor, causing less NA release from the presynaptic neuron. This decreases the effect of NA. There are also α2 receptors on the nerve terminal membrane of the post-synaptic adrenergic neuron(Fitzpatrick,et al., 2004).

There are 3 highly homologous subtypes of α2 receptors: α2A, α2B, and α2C.

Specific actions of the α2 receptor include:

Inhibition of insulin release in the pancreas.

Induction of glucagon release from the pancreas.

Contraction of sphincters of the gastrointestinal tract

negative feedback in the neuronal synapses - presynaptic inhibition of noradrenalin (NA) release in CNS

Increased thrombocyte aggregation(Large V ,et al., 1997).

β receptors

β_1 receptor

Specific actions of the β_1 receptor include:

- Increase cardiac output by increasing heart rate (positive chronotropic effect), conduction velocity (positive dromotropic effect), and stroke volume (by enhancing contractility—positive inotropic effect).
- Increase renin secretion from juxtaglomerular cells of the kidney.
- Increase ghrelin secretion from the stomach (Kline, et al., 2007).

β_2 receptor

- Specific actions of the ß2 receptor include the following:
- Smooth muscle relaxation, e.g. in bronchi, GI tract (decreased motility).
- Lipolysis in adipose tissue.
- Anabolism in skeletal muscle.
- Relax non-pregnant uterus
- Relax detrusor urinae muscle of bladder wall
- Dilate arteries to skeletal muscle
- Glycogenolysis and gluconeogenesis
- Stimulates insulin secretion
- Contract sphincters of GI tract
- Thickened secretions from salivary glands.
- Inhibit histamine-release from mast cells
- Increase renin secretion from kidney
- Relaxation of Bronchioles (salbutamol, a ß2 agonist relieves bronchiole constriction)
- Involved in brain - immune communication (kamalakkannan, et al., 2008).

β_3 receptor

- Specific actions of the ß3 receptor include:

- Enhancement of lipolysis in adipose tissue. ß3 activating drugs could theoretically be used as weight-loss agents, but are limited by the side effect of tremors (elenkov, et al., 2000).

Catecholamine Myotoxicity:

- Myocardial Contraction Band Necrosis (CBN) is the pathognomonic lesion of myocardial catecholamine damage linked with preoxidation. No systematic, quantitative studies of CNB in human and expermintal pathology were done untail we quantified this lesion in terms of number of foci and necrotic myocells .

  Baroldi et al, 2001 obtaining the followin data:

- CNB was absent in normal people who die following carbon monoxide intoxication, electrocution and head trauma while it was present in 42 % of such subjects of the latter group if they survived longer than one hour. All normal subjects died out-of-hospital, did not receive any therapy, had negative autopsy findings, their coronary arteries being normal or with insignificant atherosclerotic plaques.
- A statistically significant increase in both the frequency and extent of the lesion was recorded in acute infarct cases, transplanted heart, sudden death, and those dying of intracranial hemorrhages compared with other groups.
- There was a higher frequency and extent of CNB in people who survived longer.
- CNB had no relation to resuscitation therapy. The same extent of early lesion was observed with or without the latter.
- In groups with greater extent of CNB all morphologic stages of the lesion from early hypercontraction/rhexis to healing and healed phases was observed.

Pathogenesis of Adrenergic Storm:

The term "adrenergic" originates from "adrenaline" and describes hormones or drugs whose effects are similar to those of epinephrine. Adrenergic stress is mediated by stimulation of adrenergic receptors

and activation of post-receptor pathways. Critical illness is a potent stimulus of the sympathetic nervous system. It is undisputable that the adrenergic-driven "fight-flight response" is a physiologically meaningful reaction allowing humans to survive during evolution. However, in critical illness an overshooting stimulation of the sympathetic nervous system may well exceed in time and scope its beneficial effects. Comparable to the overwhelming immune response during sepsis, adrenergic stress in critical illness may get out of control and cause adverse effects. Several organ systems may be affected. The heart seems to be most susceptible to sympathetic overstimulation. Detrimental effects include impaired diastolic function, tachycardia and tachyarrhythmia, myocardial ischemia, stunning, apoptosis and necrosis. Adverse catecholamine effects have been observed in other organs such as the lungs (pulmonary edema, elevated pulmonary arterial pressures), the coagulation (hypercoagulability, thrombus formation), gastrointestinal (hypoperfusion, inhibition of peristalsis), endocrinologic (decreased prolactin, thyroid and growth hormone secretion) and immune systems (immunomodulation, stimulation of bacterial growth), and metabolism (increase in cell energy expenditure, hyperglycemia, catabolism, lipolysis, hyperlactatemia, electrolyte changes), bone marrow (anemia), and skeletal muscles (apoptosis). Potential therapeutic options to reduce excessive adrenergic stress comprise temperature and heart rate control, adequate use of sedative/analgesic drugs, and aiming for reasonable cardiovascular targets, adequate fluid therapy, use of levosimendan, hydrocortisone or supplementary arginine vasopressin (Rodman, et al., 1993).

Adrenaline's Heart Effects:

Adrenaline in your bloodstream achieves its effects on your heart rate by stimulating the adrenergic receptors on cells throughout your heart tissue. Once stimulated, these receptors pass the fight-or-flight message to a specialized type of protein called a G-protein. In turn, G-proteins stimulate other substances inside your cells that trigger a cascading alert effect. The overall result of this process is an increase in your heart rate, as well as an increase in the force of each individual heart contraction (Marik, et al., 2007).

Excessive Adrenalin Production

Under normal circumstances, your body will limit your fight-or-flight response to times of genuine emergency and return to normal function when appropriate. However, if your fight-or-flight response is triggered repeatedly or stays active long-term, the resulting increase in your blood levels of adrenaline and cortisol can significantly disrupt normal functional processes throughout your body. In addition to heart disease, potential consequences of this disruption include obesity, depression, and sleep disturbances, worsening of existing skin conditions, digestion problems and memory impairment (O'Brien, et al., 2007).

Brain's role in sympathetic storming:

It is believed that the Hypothalamus, a small area above the Brain Stem, that regulates body temperature, appetite and the release of hormones, over-stimulates the sympathetic nervous system by flooding the bloodstream with chemicals normally associated with stress. During this storm, the parasympathetic nervous system cannot cope and fails to control the arousal levels.

The hypothalamus itself may be damaged, or it may be responding to damage in other areas of the brain.

Symptoms of Adrenergic Storm:

The symptoms are similar to those of an amphetamine, cocaine or caffeine overdose; massive overstimulation of the central nervous system results in a state of hyperkinetic movement and unpredictable mental status; the patient may become easily enraged, or alternatively suicidal, but mania is the typical reaction.

Physical symptoms are more serious and include heart arrhythmias as well as outright heart attack or stroke in people who are at risk of coronary disease. Breathing is rapid and shallow while both pulse and blood pressure are dangerously elevated (Mayersohn, et al., 1995).

Adrenergic storm is a conglomeration of symptoms

- Hypertension.
- Tachycardia: at least 130 beats per minute
- Tachypnea: a respiratory rate of at least 40 breaths per minute
- Hyperthermia: temperature of 38.5C
- Decelerate Posturing: an abnormal body posture indicated by rigid extension of the arms and legs, downward pointing of the toes, and backward arching of the head.
- Diaphoresis: profuse sweating.
- They symptoms may vary among different individuals, along with the duration and intensity of the symptoms.
- During an episode awareness levels are generally low
- Several organ systems may be affected. The heart seems to be most susceptible to sympathetic overstimulation. Detrimental effects include impaired diastolic function, tachycardia and tachyarrhythmia, myocardial ischemia, stunning, apoptosis and necrosis. Adverse catecholamine effects have been observed in other organs such as the lungs (pulmonary edema, elevated pulmonary arterial pressures), the coagulation (hypercoagulability, thrombus formation), gastrointestinal (hypoperfusion, inhibition of peristalsis), endocrinologic (decreased prolactin, thyroid and growth hormone secretion) and immune systems (immunomodulation, stimulation of bacterial growth), and metabolism (increase in cell energy expenditure, hyperglycemia, catabolism, lipolysis, hyperlactatemia, electrolyte changes), bone marrow (anemia), and skeletal muscles (apoptosis) (Fisher, et al ., 2005).

Hypertensive crisis:

- Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110 — sometimes termed malignant or accelerated hypertension) is referred to as a "hypertensive crisis", as blood pressures above these levels are known to confer a high risk of complications. People with blood pressures in this range may have no symptoms, but are more likely to report headaches (22% of cases) and dizziness than the general population. Other

symptoms accompanying a hypertensive crisis may include visual deterioration or breathlessness due to heart failure or a general feeling of malaise due to renal failure. Most people with a hypertensive crisis are known to have elevated blood pressure, but additional triggers may have led to a sudden rise (Marik, et al., 2007).

A "hypertensive emergency", previously "malignant hypertension", is diagnosed when there is evidence of direct damage to one or more organs as a result of the severely elevated blood pressure. This may include hypertensive encephalopathy, caused by brain swelling and dysfunction, and characterized by headaches and an altered level of consciousness (confusion or drowsiness). Retinal papilloedema and/or fundal hemorrhages and exudates are another sign of target organ damage. Chest pain may indicate heart muscle damage (which may progress to myocardial infarction) or sometimes aortic dissection, the tearing of the inner wall of the aorta. Breathlessness, cough, and the expectoration of blood-stained sputum are characteristic signs of pulmonary edema, the swelling of lung tissue due to left ventricular failure an inability of the left ventricle of the heart to adequately pump blood from the lungs into the arterial system. Rapid deterioration of kidney function (acute kidney injury) and microangiopathic hemolytic anemia (destruction of blood cells) may also occur. In these situations, rapid reduction of the blood pressure is mandated to stop ongoing organ damage. In contrast there is no evidence that blood pressure needs to be lowered rapidly in hypertensive urgencies where there is no evidence of target organ damage and over aggressive reduction of blood pressure is not without risks. Use of oral medications to lower the BP gradually over 24 to 48h is advocated in hypertensive urgencies (Schmitz, et al., 1981).

Causes:

Here are several known causes of adrenergic storms; in the United States, cocaine overdose is the leading cause.[2] Any stimulant drug has the capacity to cause this syndrome if taken in excess, but even non-psychotropic drugs can very rarely provoke a reaction.

MAOIs, i.e. monoamineoxidase inhibitors, are a class of drugs that inhibit the enzyme monoamine oxidase. This enzyme is responsible for breaking down many compounds; basically, anything with a primary amine moiety is likely to be oxidized by monoamine oxidase. Important substrates of the enzyme MAO include tyrosine and tyramine, which are precursors to dopamine. MAOIs inhibit the enzyme either reversibly, in which MAO is inhibited only until the drug is cleared from the system, or irreversibly, in which the substrate binds permanently to the enzyme, rendering it inactive and effectively destroying it. These types of MAOIs are more dangerous, because the body takes about two weeks to regenerate its MAO enzymes to functional levels. There are also two subtypes of MAO: MAO-A and MAO-B; this is not relevant to adrenergic storms in any known way, but there are significant differences between the two types, such as their differential expression throughout the body and brain(Yamada, et al., 2005).

Harmine and moclobemide are two examples of reversible inhibitors; the first is a mild psychedelic used by recreational or spiritual drug users to greatly increase the bioavailability of DMT, normally entirely broken down by MAO in the stomach. The latter is an antidepressant and anxiolytic which works by reversibly inhibiting MAO-A and MAO-B, with a greater effect on MAO-A (80% inhibition) than MAO-B (30% inhibition).

With this in mind, the importance of MAOIs to adrenergic storms is that these enzymes break down substances in food that are either precursors to stimulatory drugs, or that are themselves excitatory chemicals. Aged cheese; beer; red wine; some mushrooms; fermented products such as pickles; and many other seemingly innocuous foods can provoke a hypertensive crisis. The main culprit is tyramine, a derivative of the amino acid tyrosine that is a direct precursor to dopamine. However, other substances in food can also modulate or change the effects. Hypertension will always result, however, so patients on MAOIs must be careful what they eat (Zhao, et al., 2010).

Adrenergic storms are not provoked often from MAOI-tyramine interactions; hypertensive crisis alone does not diagnose adrenergic storm, although there will always be hypertension in an adrenergic

storm, along with tachycardia and rapid, shallow breathing. However, if a patient on MAOIs uses recreational quantities of any drug with stimulant effects on the CNS, it can provoke an adrenergic crisis (along with the inevitable hypertensive crisis). Deaths have occurred from individuals attempting to combine MAOIs with various entheogens to attain a stronger psychedelic experience, both from adrenergic storms and serotonin syndrome. Combining drugs like MDMA, 2C-B, mescaline, 2C-T-7, etc. with even small quantities of MAOIs - small quantities of both drugs - is still extremely risky. Nevertheless, some users claim to use certain combinations successfully (Chen-Izu, et al., 2000)

Subarachnoid hemorrhage is an extremely serious condition in which a neural membrane is breached and the brain itself is compromised. The onset is sudden, described as "the worst headache of one's life," and many grave symptoms follow. Adrenergic storm is often present among these symptoms, and is responsible for some of the dangers, both long-term and short, of subarachnoid hemhorrhage adrenergic storm, through a complex cascade of processes starting with the movement of subarachnoid blood into the brain. Apparently, as the intracranial pressure increases, the brain is squeezed and catecholamines are forced out of their vesicles into the synapses and extracellular space. An alternative explanation that has been proposed is that this increased in intracranial pressure transduces through the brain parenchyma through to the blood vessels producing a loss in effective cerebral perfusion. This triggers the sympathetic nervous system to secrete more norepinepherine and epinepherine increasing blood pressure and heart rate to dangerous levels in order to maintain cerebral perfusion (Rodman, et al., 1993).

Rarely, a pheochromocytoma (tumor of the medullar tissue of the adrenal glands, which are located anterior to the kidney), may result in an adrenergic storm. This type of tumor is not common to begin with, and furthermore, the subtype that can cause massive adrenaline release is rarer still. Patients with pheochromocytoma can unexpectedly fly into a rage or sink into trembling fear, possibly dangerous to themselves and others as their judgment is impaired, their senses and pain threshold are heightened, and the level of the adrenalin in their bloodstream is

more than most people ever experience; pheochromocytoma can, very rarely, kill by internal adrenaline overdose. But overall, adrenergic storm is an uncommon but certainly not rare phenomenon associated with the unfortunate but also uncommon condition of pheochromocytoma (Whalen, et al., 1992).

Differential diagnosis:

Because the adrenergic storm overlaps with so many other similar conditions, such as hypertensive crises, stimulant intoxication or overdose, or even panic attack, and because the treatments for these overlapping conditions are largely alike, it is not necessary to obtain a differential and definitive diagnosis before initiating treatment. However, analysis of the patient's medical history, checked against the possible causes of the adrenergic storm such as those above, should be done, because some adrenergic storms can be caused by serious underlying conditions. If a patient has an adrenergic storm and all or most of the other factors are ruled out, the adrenergic storm could lead to the discovery of a pheochromocytoma, which can become malignant. However, not all cases of adrenergic storm have an identifiable cause. Like a seizure, sometimes a patient has a single one, or perhaps a few, and then does not for the rest of their life. The mechanisms of idiopathic adrenergic storm are very poorly understood.

Serotonin syndrome, in which an excess of serotonin in the synapses causes a similar crisis of hypertension and mental confusion, could be confused with an adrenergic storm. The difference is that serotonin, being a tryptamine (non-catecholamine) involved in higher brain functions, can cause dangerous hypertension and tachycardia from its effects on the sympathetic nervous system, but as there are no serotonin receptors in the heart or blood vessels there are no direct effects on the heart. Thus, the presence of arrythmia, abnormal echocardiograms, or chest pain indicates an adrenergic crisis and rules out serotonin syndrome.

- Strum et al defined storming as a diagnosis of exclusion in patients who had recurrent spontaneous episodes of tachycardia, hypertension, and hyperthermia.

- Baguley et al, required that 5 of 7 clinical features(tachycardia, hypertension, tachypnea, hyperthermia, dystonia, posturing, and diaphoresis) be present.
- Blackman et al, required that signs and symptoms occur a minimum of 1 cycle per day for 3 consecutive days in a patient with severe brain injury (level on Ranchos Los Amigos Scale ≤ IV)
- Ranchos Los Amigos scale ≤ IV indicates sympathetic storming

Level	Description
I	No response to visual, verbal, tactile, auditory, noxious stimuli
II	Generalized response
III	Localized response
IV	Confused-agitated
V	Confused-inappropriate
VI	Confused-appropriate
VII	Automatic-inappropriate
VIII	Purposeful and appropriate
IX	Purposeful and appropriate (standby assistance on request)
X	Purposeful and appropriate (modified independent)

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Outcome of adrenergic storm:

- Catecholamine storming is associated with increased risks of
- Death
- Cardiac arrest
- Cerebral haemorrhage or elevated cerebral temperature, which can itself lead to secondary injury.
- Rhabdomyolysis due to Severe muscle rigidity which results in muscle rupture or the breakdown of muscle fibres
- Increased length of stay in rehabilitation services and less favorable rehabilitation outcomes.

- Prolonged hypertension, arrhythmias, hyperglycemia, hyperthermia due to elevated metabolic rate, and hypernatremia from severe diaphoresis occur as a result of the sympathetic storm.

Treatment:

- If an overdose by ingestion is suspected, the patient should be given gastric lavage, activated charcoal, or both; this could make the difference between life and death in a close situation, but it should be avoided unless there is evidence of overdose as it can aggravate the patient.
- The first line treatments are diazepam and a non-selective beta blocker; other antihypertensive drugs may also be used. Not all benzodiazepines and beta blockers are safe to use in an adrenergic storm; for instance, alprazolam and propranolol; alprazolam weakly agonizes dopamine receptors and causes catecholamine release while propranolol mildly promotes some catecholamine release.
- After bringing the heart rate and blood pressure down, treatment is supportive; if there is an underlying condition causing the adrenergic storm, then that must be addressed. However, many cases of adrenergic storms are completely idiopathic in nature; indeed, they are a poorly understood phenomena (Jones, et al., 1996).

Sympatholytic

A sympatholytic (or sympathoplegic) drug is a medication which inhibits the postganglionic functioning of 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.

Antiadrenergic:

Antiadrenergic agents inhibit the signals of epinephrine and norepinephrine. They are primarily adrenergic antagonists, (Alpha Blockers and Beta Blockers) inhibiting adrenergic receptors, but, there are exceptions: clonidine is an adrenergic agonist on the α2 receptor, since this receptor is located presynaptically to inhibit further release of adrenaline and noradrenaline.

Other ways of inhibiting adrenergic signaling is by catecholamine synthesis blocking, e.g. by methyltyrosine. Reserpine works by inhibiting transport into synaptic vesicles of noradrenaline by inhibiting the VMAT.

Many antiadrenergic agents used as antihypertensives include:

- centrally acting:
- Clonidine (α2 agonist)
- Guanfacine (α2 agonist)
- Methyldopa (α2 agonist)
- Moxonidine (imidazoline receptor agonist)
- Prazosin (α1 antagonist)
- Rescinnamine (ACE inhibitor)
- Reserpine (VMAT inhibitor)
- Rilmenidine (imidazoline receptor agonist)

Ganglion-blocking

- Mecamylamine (α3β4 nicotinic receptor antagonist)
- Trimethaphan (ganglion type receptor antagonist)

Peripherally acting

- Guanethidine (Magnesium-ATPase inhibitor)
- Indoramin (α1 antagonist)
- Doxazosin (alpha blocker)

- Beta Blocker
    - Non-selective agents

- Alprenolol
- Bucindolol
- Carteolol
- Carvedilol (has additional α-blocking activity)
- Labetalol (has additional α-blocking activity)
- Nadolol
- Penbutolol (has intrinsic sympathomimetic activity)
- Pindolol (has intrinsic sympathomimetic activity)
- Propranolol
- Sotalol
- Timolol

- β1-Selective agents

- Acebutolol (has intrinsic sympathomimetic activity)
- Atenolol
- Betaxolol
- Bisoprolol
- Celiprolol
- Esmolol
- Metoprolol
- Nebivolol

- β2-Selective agents

- Butaxamine (weak α-adrenergic agonist activity) - No common clinical applications, but used in experiments.
- ICI-118,551 Highly selective β2-adrenergic receptor antagonist - No known clinical applications, but used in experiments due to its strong receptor specificity.

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 (Tryer, 1992).

Some people have used beta blockers for 'performance anxiety'. 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.

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) (Tryer, 1992).

Although they have no recognisable 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 metre pistol silver medallist and 10 metre air pistol bronze medallist Kim Jong-su tested positive for propranolol and was stripped of his medal.

Post traumatic stress disorder (PTSD) is theorized to be the result of neurological patterns caused by adrenaline and fear in the brain. By administering beta blockers immediately following a traumatic event, as well as over the next couple weeks, the formation of PTSD has been reduced in clinical studies (Tryer, 1992).

Alpha Blockers:

Alpha Blockers 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 (Kaplan ,1998). 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 (Harmon and Riggs 1996). Insomnia and nightmares were also reported to be reduced.

Kinzie and Leung (Kinzie and Leung, 1989).

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 (Horrigan and Barnhill 1996).

A recently completed randomized double-blind trial among veteran patients with chronic PTSD showed that augmentation with guanfacine was associated with improvement in anxiety and PTSD.

Prazosin is an alpha1-receptor antagonist. Raskin and colleagues (Raskind, et al., 2003)

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 .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.

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