How to reduce endogenous adrenaline synthesis in patients with a dysfunctional renal medulla using an APZ-BMZ-DXM combination therapy - preliminary report

Dr. Carolina Diamandis[1], Riku Honda[1], Fabio Rocha[1], and Ali Shirazi[1]

[1]Affiliation not available

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Abstract

Adrenaline, also known as epinephrine, is a hormone and neurotransmitter produced by the adrenal gland. It is an essential component of the fight-or-flight response, a survival mechanism that prepares the body to respond to perceived danger. When the body experiences stress, the hypothalamus activates the adrenal gland's medulla, which releases adrenaline into the bloodstream. However, some people suffer from chronically elevated hyperadrenergic conditions, mostly secondary to another disease. These conditions can lead to a wide range of symptoms, including anxiety, panic attacks, heart disease, tremors, sweating, and difficulty sleeping. In severe cases, it can even lead to heart failure, stroke, and death. The reduction of endogenous adrenaline synthesis is an important part of managing hyperadrenergic situations. Endogenous adrenaline refers to the adrenaline produced by the body, as opposed to exogenous adrenaline, which is adrenaline that is taken as a medication. By reducing the amount of adrenaline produced by the body, it is possible to relieve the symptoms of hyperadrenergic conditions and improve the quality of life for those affected. This preliminary paper presents a new medication regimen which is, to our knowledge, the most effective one so far.

MILAD MEDICAL RESEARCH
MILAD HEALTH CENTER DR. SHIRAZI - TEHRAN - IRAN

Carolina Diamandis[1], Riku Honda[3], Fabio Rocha[3], Ali Shirazi[2]
1) LCG Greece Research
2) Milad Health Complex
3) NWO Tokyo

Corresponding author:
Dr. Ali Shirazi's Lab. Milad Medical Complex, Tehran, Iran
dr.ali.hosseini@yandex.com

ENDOCRINOLOGY

How to reduce endogenous adrenaline synthesis in patients with a dysfunctional renal medulla using an APZ-BMZ-DXM combination therapy - a preliminary report.

Abstract

Adrenaline, also known as epinephrine, is a hormone and neurotransmitter produced by the adrenal gland. It is an essential component of the fight-or-flight response, a survival mechanism that prepares the body to respond to perceived danger. When the body experiences stress, the hypothalamus activates the adrenal gland's medulla, which releases adrenaline into the bloodstream. However, some people suffer from chronically elevated hyperadrenergic conditions, mostly secondary to another disease. These conditions can lead to a wide range of symptoms, including anxiety, panic attacks, heart disease, tremors, sweating, and difficulty sleeping. In severe cases, it can even lead to heart failure, stroke, and death. The reduction of endogenous adrenaline synthesis is an important part of managing hyperadrenergic situations. Endogenous adrenaline refers to the adrenaline produced by the body, as opposed to exogenous adrenaline, which is adrenaline that is taken as a medication. By reducing the amount of adrenaline produced by the body, it is possible to relieve the symptoms of hyperadrenergic conditions and improve the quality of life for those affected. This preliminary paper presents a new medication regimen which is, to our knowledge, the most effective one so far.

Adrenaline excess

An endogenous adrenaline (also known as 'epinephrine' in the U.S.) excess can have a range of dangerous effects on the entire body. It increases the heart rate and blood pressure, expands the air passages of the lungs, enlarges the pupils in the eyes, and causes constriction of peripheral blood vessels. It also mobilizes energy stores in the form of glucose and free fatty acids instantly during times of stress or danger, prepares the body to fight or flee and stimulates glycogenolysis and glycolysis in muscles.[1-7]

Symptoms of endogenous adrenalin excess can include fatigue, muscle loss, palpitations, heart muscle damage, sweating, and difficulty breathing. It can also cause chaos in the body's stress axes up to a total breakdown of homeostasis, and is crucial for the autonomous regulation of respiration. The long term effects of chronic adrenalin excess include anxiety, depression, digestive problems, headaches, muscle tension and pain, heart disease, heart attack, high blood pressure, palpitations, shortness of breath, sudden onset headaches, sweating, hyperglycemia, tremor and anxiety.[4-7]

Adrenaline makes the heart pump faster and more powerful by directing blood flow to it, but it also causes constriction of small blood vessels which can reduce blood flow to other organs, including the brain, and may lead to neurological damage. Over time, high levels of adrenaline can increase the risk of hypertonia, heart attacks, strokes, and cause heart arrhythmias, heart failure, anxiety and panic disorders and many more conditions. Adrenaline increases the heart rate, strengthens the force of the heart's contraction, shortens the isometric contraction phase reliably, accelerates the speed of contraction, and increases LV systolic emptying while in the long run this is one of the ways by which adrenaline contributes to the dangerous development of a progressive and chronic 'congestive' heart failure.[3]

Over time, high levels of adrenaline can also trigger weight loss, let the the ability to focus on a topic drop significantly and reduces the measurable IQ. Additionally, adrenalin and cortisol increase the level of sugar in the bloodstream which can lead to diabetes types 2 and 3.[4-8]

Therefore, chronic adrenalin excess needs to be treated with a combination of treatments depending on the exact cause. Adrenaline itself is used to treat multiple conditions in an emergency setting very effectively. However, chronic stress or anxiety that prevents rest at night can also lead to an adrenaline rush and organic diseases of the renal medulla which causes chronically elevated levels of adrenalin which leads to an endless number of highly dangerous conditions in a vicious circle.[3,6,7]

Long-term effects of chronic adrenalin excess can also include panic without a psychological reason, anxiety, depression, digestive problems, headaches, muscle tension and pain, heart disease, heart attack, high blood pressure, sleep difficulties, severe hormonal problems, hypothyroid type symptoms like cold intolerance, sluggish metabolism and weight gain. An adrenaline rush can last up to an hour in a situations of real danger (necessary) or it can become chronic (permanent and dangerous).[3,4,6,8]

Most commonly excess of adrenaline is caused by chronic stress, an adrenal tumor

or autoimmune and storage diseases like amyloidosis or iron storage disorders.[4,5,6,7]

Endogenous adrenaline synthesis

Adrenaline is produced in the medulla of the adrenal glands and some neurons in the central nervous system. The very small renal medulla also produces other highly important substances such as norepinephrine (noradrenaline), hormones of the renin-angiotensin system (RAS), 1.25-dihydroxyvitamin D3, as well as renin and angiotensin. Adrenaline is released into the blood during times of stress or danger, preparing the body for 'fight or flight'. The adrenal medulla is responsible for producing catecholamines, such as epinephrine and norepinephrine. Adrenaline is synthesized in the chromaffin cells of the adrenal gland's adrenal medulla and a small number of neurons in the medulla oblongata in the brain through a metabolic pathway that converts the amino acids phenylalanine and tyrosine into a series of metabolic intermediates and, ultimately, adrenaline.
In healthy individuals it is released into the body during times of stress or danger and plays an essential role in the body's commonly known life-saving 'fight-or-flight' in humans and many animals. It triggers the body's fight-or-flight response, causing air passages to dilate to allow more oxygen into the lungs, increasing heart rate and force of heart contractions, increasing blood flow to the muscles, organs and to the brain, as it also up-regulates glucose metabolism. It also helps control salt balance in the blood (together with aldosterone) and glucose level balance (together with cortisol). The effects of adrenaline increase the heart rate instantly and triggers strong heart contractions, expands the air passages of the lungs, and redirects blood toward major muscle groups. Over time, high levels of adrenaline can, therefore, increase the risk of a heart attack or stroke, cause heart disease, high blood pressure, anxiety, panic, weight gain, mental disorders, erectile dysfunction, vascular spasms etc.[3-7]

Is a targeted therapeutic reduction of the endogenous adrenaline synthesis in the renal medulla possible?

Until 2022, there was no medication or treatment protocol available which could be used to directly and significantly reduce the adrenaline synthesis in the renal medulla. This is because the adrenal medulla secretes hormones such as adrenaline and noradrenaline to help the body respond to stress, and these hormones are regulated by other endocrine glands. Furthermore, recent research has suggested that more renal metabolism pathways plays an important role in hypertension development, making it difficult to target a single medication for reducing adrenaline synthesis.[3,8]

Until our research results, there were no medication regimens known which target adrenaline synthesis in the renal medulla.

Trials with nitrates, alpha-blocking agents and diuretics were used to reduce the pressor effects of adrenaline, and hypoxia signaling has been shown to have an impact on adrenal hormones, however, until 2022 adrenal over-production due to a distorted renal medulla was not directly treatable. The only way to protect the body was the use of competitive receptor blocking agents (e.g. beta-blockers) which bind to the very receptors adrenaline would also bind. Through this competitive situation the effect of a chronic adrenaline excess can be influenced, however, all other

damaging effects of chronically elevated adrenaline levels were hard or impossible to treat.[4,6,7,8]

A new and successful approach using a combination therapy of three well-knows medical drugs

This situation has changed in 2022 when a team at the Milad Medical Research Center tried a combination therapy on 30 male and 30 female volunteers, all of them healthy healthcare workers aged 21 to 55 (39 years in average) after informed consent and an extraordinarily thorough medical examination. The effect result of the regimen was astonishing: the synthesis of the endogenous adrenalin synthesis in the volunteers' renal medulla was highly significantly reduced (peak low values) by an average of 53.2% (30.8 to 80.9%) as soon as three to latest five days after the treatment began. It remained at that level until the test was ended after ten days with tapering down the medication over a timespan of five days.

All volunteers returned to their normal individual natural adrenalin synthesis which had been measured before the trial, latest after two to six days. No volunteer showed any severe undesirable effects or any type of significant permanent effect or health damage. Despite the unfortunate lack of a placebo group the effects were too massive, similar and impressive to be explainable with anything else than the tested medication regimen.

The APZ-BMZ-DXM protocol does lower the endogenous adrenalin synthesis in the renal medulla

Based on the brilliant works of Breier 1992, Stratton & Halter 1985, and Fries 2006, a team led by Ali Shirazi, Ali Hosseini and Riku Honda has put together a medication regimen of already approved drugs that specifically targets five goals:

- The activity of the renal medulla.
- A stabilization of the HPA axis.
- The sigma and glutamate receptors in the brain in order to target specific functions of the hippocampus.
- Using already existing drugs that are well tolerated and relatively safe.
- A rapid onset of at least 75% of the peak effect within a couple of minutes to hours.

Since this paper is a pre-publication, the exact biological effects will be outlined in the final journal version at this point.

The volunteer subjects received 2 mg alprazolam (APZ), 3 mg bromazepam (BMZ), and 50 mg dextromethorphan (DXM) every 6 hours, the latter in sustained release form. Adrenaline levels in the blood and all relevant metabolites in the urine were measured precisely every 12 hours.

The results far exceeded the expected effects by far. No other drugs regimen has ever shown an average reduction of endogenous adrenaline synthesis in the renal medulla by 53.2% (30.8 to 80.9%). All this with old, well-tested, inexpensive and generally very well-tolerated drugs. Excessive daytime sleepiness was also less observed than expected. This was most likely due to the mood-stabilizing and activating effect of dextromethorphan which has strong psychotropic effects in higher doses. Cessation of one of the substances for test purposes led to the disappearance of the adrenaline inhibitory effect in a short time, depending on the

serum level and the half-life (see tables 1 to 6).

PLACEHOLDER
for Tables 1 to 6 in the journal version.

Alprazolam (APZ)

The medical drug Alprazolam (original brand name Xanax) is a benzodiazepine used to treat anxiety and panic disorders with an unjustified bad reputation since it has been abused in the Unites States, especially before the onset of the current opioid crisis in North America. It is a well tolerable medical drug which reduces the synthesis of adrenaline in the renal medulla, according to the available literature by 40-70%, thus making it an effective choice for treating anxiety and panic disorder due to organic, non-psychological causes.

Alprazolam is therefore unique and superior to other benzodiazepines in the treatment of panic disorder. Other benzodiazepines mainly used for anxiety like lorazepam and diazepam have no impact on the renal medulla whatsoever and are useless as adrenaline synthesis inhibitors.

However, high doses of alprazolam can cause sudden-onset aggression and inadequate behavior. Therefore the stress-axes and the brain activity level as such has to be calmed down with another drug: bromazepam.[4,5,8]

Bromazepam (BMZ)

Bromazepam is a also a benzodiazepine that has been shown to be effective in reversing anxiety-like behavior with a focus on relaxation and calming down patients. It works by strongly affecting GABA receptors and by binding to hippocampal glucocorticoid receptors (GRs) which inhibit the paraventricular nucleus (PVN) of the hypothalamic-pituitary-adrenal (HPA) axis. The PVN releases two hormones, anti-diuretic hormone (ADH) and corticotropin releasing factor (CRF), which initiate the hormone cascade of the HPA axis. This stabilization of one of the main stress axes helps to reduce stress responses of any kind.[4,5,8]

Apart from a relevant addiction risks that is considered normal in benzodiazepines (despite the fact that about 45% of all patients do not develop a severe form of addiction, genetic factors might play a role in this issue), bromazepam has a relatively long half-life, and is a quite benign drug that has been prescribed for many decades, especially in Europe and Asia. In combination with alprazolam, it effectively blocked the oftentimes very unpleasant aggression inducing side effects in all our volunteer subjects.[4,5,6]

Dextromethorphan (DXM)

Widely used Dextromethorphan (DXM) has been shown to reduce oxidative stress and inhibit NADPH oxidase activity which can help to moderate the behavioral effects of stress in vivo. DXM also has a demulcent effect, which is further enhanced by its antioxidant properties. Most interestingly, dextromethorphan (DXM) is a moderate but very fast acting serotonin reuptake inhibitor and can promote immediate serotonin release with

an instant-onset relaxing effect. DXM has multi-faceted pharmacodynamic and pharmacokinetic properties and acts as an NMDA receptor antagonist as well as it interferes with the sigma receptors in the brain, affecting signaling pathways to the hippocampus. DXM also blocks N-methyl-d-aspartate (NMDA) receptors and inhibits the reuptake of glutamate, among a series of other mechanisms.[4,5]

Conclusion

Our preliminary data demonstrate a quite strong inhibitory effect on the endogenous synthesis of adrenaline in the renal medulla with a regimen of alprazolam, bromazepam, and dextromethorphan (APZ-BMZ-DXM). Under professional medical supervision, this drug regimen is well tolerated and can be considered essentially safe. Self-treatment is not an option, however, as these substances are highly potent drugs with the risk of developing an addiction which would be extremely hard to treat. However, it is a milestone that now this regimen provides clinicians with an easy-to-use, relatively safe and inexpensive medication for the first time. It can effectively help patients suffering from pathologically increased endogenous adrenaline synthesis that is not caused by a tumor.

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Conflicts of interest

None

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