3.2.2.3.6.8 How yohimbine and sildenafil citrate (Pfizer’s Blue) work

For erections to occur there must be vasodilation of penile tissue. All medications for erectile dysfunction have a vasodilation effect. But apart from this, erectile dysfunction medications work very differently. It is anyway surprising how many physiological processes, which are quite independent from each other, actually contribute to erections.

Sildenafil citrate works on an enzymatic level. It suppresses the enzyme phosphodiesterase type 5 (PDE5), which naturally occurs in erectile tissue. Phosphodiesterase type 5 (PDE5) breaks down the body chemical known as cyclic GMP. Cyclic GMP is produced during arousal and causes muscular and vascular changes, which lead to an erection. Men who don’t produce a sufficient amount of cyclic GMP will have problems achieving an erection. Likewise, men with high levels of the enzyme phosphodiesterase type 5 (PDE5) will have problems maintaining one.

Sildenafil citrate doesn’t produce the same results in all men. This is the case because for cyclic GMP to do its job in the first place, there have to be specific receptors. Men whose genetic program provides for a comparative generous number of receptor sites for cyclic GMP are likely to produce better erections than those with a smaller number. It’s a variation in the human race that cannot be corrected by sildenafil citrate.

Tongkat ali’s vasodilating effect is based on the neurotransmitter nitric oxide, which generates cyclic GMP. Tongkat ali’s effect is a chain of events that oscillates between the genitals and the brain. The chain reaction starts with tongkat ali stimulating the Leydig cells of the testes to increase testosterone production.

Increased levels of testosterone also cause levels of the neurotransmitter dopamine to rise. Both testosterone and dopamine tends to effect associative regions of the brain in a way that focuses attention on sexual desires and sexual imaginations. Via nitric oxide, these effects of arousal lead to the proliferation of cyclic GMP in the genital area, thus causing erections (the effect will not be obtained with tongkat ali products of inferior quality; a single dose of tongkat ali extract should be the equivalent of 50 grams of tongkat ali root).

The vasodilation effect of yohimbine is based on an entirely different physiological mechanism. The Mosby RxList reference to pharmaceutical drugs describes yohimbine as follows (this description is practically identical with the package brochure text of some prescription yohimbine brands).

“Yohimbine blocks presynaptic alpha-2-adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine’s peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade, which may theoretically result in increased penile inflow, decreased penile blood outflow or both. Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

“Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by beta-adrenergic receptors; its effect on blood pressure, if any would be to lower it; however, no adequate studies are at hand to quantitate this effect in terms of yohimbine dosage.”

Contrary to the above quote, there are scientific studies that have shown that under certain conditions, yohimbine can indeed result in a rise of blood pressure. The Expanded Commission E Monographs, published by the American Botanical Council list hypertension as a possible side effect:

“Therapeutic administration of yohimbine can cause nervous excitation, tremor, sleeplessness, anxiety, increased blood pressure, tachycardia, nausea, and vomiting. In case of existing liver and kidney diseases, yohimbe preparations should not be used. Interactions with psychopharmacological herbs have been reported.”

To understand the pharmacological action of yohimbine, the following has to be considered.

A large number of bodily (physiological) processes are outside of a person’s voluntary control. They are controlled by the autonomic nervous system. This includes for example breathing, digestive processes, heartbeat, and blood pressure. Much of the autonomic nervous system functions as two pathways, the sympathetic and the parasympathetic nervous system. These two parts of the nervous system largely use separate but parallel nerve cords.

The sympathetic division is responsible for the body’s reaction to stress factors. When the sympathetic system is active, heart rate and blood pressure will increase, respiration becomes faster, blood vessels to the heart will be dilated, and there will be increased blood flow to the muscles. This is, by and large, accompanied by a constriction of arterial blood vessels.

The parasympathetic division rules in restful situations. When stress situations subside, parasympathetic nerve impulses will slow the heart rate and decrease blood pressure, slow breathing, stimulate digestion, induce salivation, and dilate peripheral blood vessels.

For nerve impulses from the brain or central nervous system to reach their destinations, they have to be transmitted from nerve cell to nerve cell on a specific pathway. The transmission between nerve cells is effected by neurotransmitters, which are emitted by an upstream nerve cell. For the signal to reach the next downstream nerve cell, there have to be synaptic receptors on which neurotransmitters can dock.

The neurotransmitter active on the sympathetic pathway is norepinephrine. The neurotransmitter active on the parasympathetic pathway is acetylcholine. Norepinephrine is not just a

neurotransmitter but also a hormone; it is secreted by the adrenal glands. While neurotransmitters only have the function to connect nerve cells, hormones are messenger molecules that act on body parts at some distance from where the hormone originates.

In contrast, prostaglandins are messenger molecules that act in the environment where they originate. A prostaglandin that effects vasodilation of penile tissue is alprostadil (prostaglandin E1). Alprostadil cream is an additional medication that can be used to induce erections.

A large number of neurologically active pharmaceuticals actually do not affect nerve cells themselves but rather the neurotransmitters in between. Yohimbine is such a pharmaceutical. It blocks the receptor sites for the neurotransmitter norepinephrine. More specifically, yohimbine blocks presynaptic alpha-2-adrenergic receptors. By thus interfering with the sympathetic nervous system, the parasympathetic nervous pathway will prevail in controlling a large number of involuntary bodily functions. Peripheral vasoconstriction (a tightening of blood vessels in the extremities) will be hindered, resulting in more blood flow to those extremities. Among the extremities that benefit from this condition is the male erectile organ. Other symptoms of the parasympathetic nervous system being in charge are the increased salivation as well as the increased digestive activity usually noticed when on yohimbine.

Adrenergic blockade can be effected not just by yohimbine but a considerable number of other pharmaceutical agents as well. And those other pharmaceutical agents do not work as aphrodisiacs or medication against erectile dysfunction. Actually, most adrenergic blockage drugs, such as so-called beta-blockers are known to impair sexual function.

To evaluate the effect of the adrenergic blockage caused by yohimbine, we have to be aware of the differentiation among adrenergic receptors. Four different kinds of receptors have been identified: alpha-1, alpha-2, beta-1, and beta-2. They all are binding sites for the adrenal hormone / neurotransmitter epinephrine. All except for beta-2 receptors are also docking sites for norepinephrine. As the adrenal hormones are practically the same for all receptors, the differentiation is effected by the different receptors.

Heart function and blood pressure are more closely correlated to beta-receptors than to alpha-receptors. Your typical medication for high blood pressure is a beta-blocker.

Beta-blockers are known to cause erectile dysfunction, and the reason is probably the same that answers why yohimbine can cause tachycardia (an abnormally fast heart beat). If epinephrine and norepinephrine are artificially prevented from docking at beta receptors (or alpha-2 receptors), this will result in elevated plasma levels of norepinephrine and epinephrine. The hormone / neurotransmitter will then exhibit an increased tendency to bind to those receptor sites that have not been blocked.

Therefore, it is reasonable to assume that in the case of beta-blockers, there will be an increased pressure on alpha-receptors to accommodate the circulating epinephrine and norepinephrine. Alpha-2 receptors have a major function in erections in that epinephrine and norepinephrine have to be evicted from alpha-2 receptors in order for erections to occur. However, the presence of higher plasma levels of epinephrine and norepinephrine (because of a lack of possibility to dock on beta receptors) will make this more difficult to achieve. Therefore, while beta-blockers cause a decrease in blood pressure and slow down the heart, the adrenergic effect on some peripheral organs, including erectile tissue, is increased. Therefore, beta-blockers have a tendency to cause erectile dysfunction.

Like beta-blockers, alpha-blockers such as yohimbine will cause an increase in plasma levels of the adrenal hormones / neurotransmitters epinephrine and norepinephrine. And if the epinephrine and norepinephrine cannot dock at alpha-2 receptors, there will be an increased tendency to dock at beta-1, beta-2, and alpha-1 receptors. This can lead to hypertension and tachycardia (an abnormally fast heartbeat).

Most of the literature on yohimbine recommends daily use, in order to keep unwanted side effects like nervousness and insomnia at bay. The rationale for such a recommendation is derived from basic facts of the endocrine system.

Practically all hormones have the effect of inhibiting their own

production, usually via negative feedback carried through blood plasma to the hypothalamus-pituitary axis. The adrenal hormones / neurotransmitters epinephrine and norepinephrine are no exception.

The hypothalamus measures plasma levels of epinephrine and norepinephrine (as well as plasma levels of most other hormones from the adrenals or other glands); if plasma levels are high, no action is taken; if plasma levels are low, the hypothalamus releases Corticotropin-releasing hormone. Corticotropin-releasing hormone then stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH, corticotropin). Corticotropin then stimulates the adrenals to secret adrenal hormones.

The few physicians who do subscribe yohimbine in the age of phosphodiesterase inhibitors usually tell their patients that problems such as restlessness and insomnia subside after several days into a yohimbine cycle. The following could explain what happens.

On the first days of yohimbine ingestion, plasma levels of epinephrine and norepinephrine are artificially high. They remain high until either the alpha-2 adrenergic blockage has been removed (thus again allowing dockage at these receptors, or until elevated plasma epinephrine and norepinephrine will have been dealt with by the liver. As the hypothalamus definitely senses elevated epinephrine and norepinephrine plasma levels, there will, during the first days on a yohimbine cycle, likely be no release of corticotropin-releasing hormone by the hypothalamus, and therefore no release of corticotropin by the pituitary, and thus no additional release of norepinephrine and epinephrine by the adrenal medulla.

Therefore, when into a yohimbine cycle, it is reasonable to assume that the release of epinephrine and norepinephrine will be down-regulated by the hypothalamus , but only with continuous use.

Apart from presynaptic alpha-2-adrenergic receptor blockade, there may be other elements that contribute to the sexuality and erection enhancing power of yohimbine, though presynaptic alpha-2-adrenergic receptor blockade is probably the most relevant element. It has been noted that yohimbine has an anti-diuretic action, probably via the release of the posterior pituitary hormone vasopressin or even via anti-diuretic hormone (ADH). Vasopressin is also available

as pharmaceutical product, and as such, it is sometimes used for its sexually stimulating effect. One can assume that the probable release of vasopressin contributes to the sexually stimulating effect of yohimbine. Yohimbine also has an effect on MAO inhibition (covered in another article).