3.2.2.3.6.3 Yohimbine pharmacology

Many people have the impression that, with thousands of medications stocked at a well-sorted pharmacy, we have the power to interfere with human physiology in thousands of ways, each specific to a certain medication.

But this impression is wrong. The scope of what can be achieved with medications in general is much narrower than commonly believed.

There are a few well-established fields in which we can achieve a physiological effect through pharmacological means, and these windows of therapy are widely exploited for the treatment of a wide range of conditions, and with dozens or hundreds of medications that all basically have a similar effect.

One such window for pharmacological interference is the modulation of neurotransmitters.

Neurotransmitters are chemical substances through which messages are communicated between neurons (nerve cells). Neurotransmitters regulate a large number of physiological processes, with the main options being to speed them up or to slow them down. Some neurotransmitters have a dual function as hormones, for example epinephrine (also named adrenaline).

The difference between hormones and neurotransmitters is that hormones travel to rather distant target tissue via the blood stream (which takes time) while neurotransmitters just bridge the synapses (gaps) between neurons.

The result of the activities of epinephrine (adrenaline) as a neurotransmitter and as a hormone is similar: the body is prepared for stress or activity.

Epinephrine is synthesized by body enzymes in several steps from the amino acid tyrosine, which is turned into dopa, then dopamine, then norepinephrine, then epinephrine. Dopamine and norepinephrine have a wider function as neurotransmitters than does epinephrine. The three are grouped as catecholamines.

Major neurotransmitters apart from the catecholamines are serotonin and acetylcholine, both of which roughly have slowing-down functions.

A multitude of conditions are treated by interfering with neurotransmitters.

Practically all anti-depression medications work by up-regulating neurotransmitters. The newer anti-depression drugs such as Prozac up-regulate the neurotransmitter serotonin by interfering with its re-uptake (storage for later use in vessels at the nerve endings); these drugs are named SSRIs, or selective serotonin re-uptake inhibitors. Older anti-depression medications such as trazodone are less specific in scope and work by elevating neurotransmitter levels pretty much across the board. Herbs such as St. John's wort also work through several neurotransmitters.

Other, older, anti-depression medications which have run out of favor because of potentially life-threatening side effects are the so-called MAO inhibitors (monoamine oxidase inhibitors). Catecholamine neurotransmitters (dopamine, norepinephrine, and epinephrine) are monoamines. By interfering with their degradation (enzymatic oxidation) MAO inhibitors cause elevated levels of dopamine, norepinephrine, and epinephrine.

Broadly speaking, elevated levels of neurotransmitters cause happiness in various degrees and forms. The aim of anti-depression medications is to assure levels that are high enough to avoid that people feel frustrated, sad, hopeless, or suicidal.

Most pleasure drugs or drugs of abuse owe their value as such to the fact that in one way or another, they increase neurotransmitter levels, often drastically. Cocaine, amphetamine, and methamphetamine all strongly build up dopamine levels. Ecstasy and LSD primarily work on the serotonin pathway.

It’s in a way amazing how our mental states depend on levels of neurotransmitters. You can be about to die from cancer or a bad injury. If you are allowed to inhale some crack cocaine at that time, you can be sure to mentally have a positive outlook, even though your immediate and long-term future lies in a grave.

Elevating neurotransmitters, mainly catecholamines, plays a major role not only on the street drug scene but also in enhancing performance in sports. The terms “dope” and “doping” are both obviously related to the name “dopamine”.

There are many other, legitimate, uses of interfering with neurotransmitters.

Some treatments of respiratory emergencies, e.g. asthma, rely on the neurotransmitter / hormone epinephrine which, among other effects dilates bronchioles, thus allowing more breath intake.

A very large number of cardiac drugs and drugs to control blood pressure depend on interfering with epinephrine (adrenaline), primarily in its function as a hormone. Epinephrine as a hormone, like norepinephrine and epinephrine as neurotransmitters, prepares the body for fight or flight. They increase blood pressure and heart rate and up-regulate the blood and oxygen supply to muscle tissue.

A good number of medications used to reduce heart rate and blood pressure aim to down-regulate epinephrine’s hormonal effects. They do their work by locking and blocking the receptors for epinephrine (adrenaline) in cardiac and vascular tissue.

All hormones only can do their job when the tissue they meet on their travels through the human body is capable of receiving their chemical signals. This means, hormone receptors have to be present. There are numerous receptors for hormones throughout the body. Those receptors that are capable to receive signals from epinephrine (adrenaline) have been named adrenergic. There are two main groups of adrenergic receptors, named alpha and beta receptors. There are sub-groups to both of them, such as alpha-1 adrenergic receptors, alpha-2 adrenergic receptors, beta-1 adrenergic receptors, beta-2 adrenergic receptors. The receptors in heart tissue which, when docked at by epinephrine (adrenaline) are responsible for increased heart rate primarily are beta receptors.

If these beta receptors are locked and blocked, epinephrine / adrenaline (as hormone) can no longer do its job to increase heart rate. Because of their mode of action, these drugs are named beta-blockers, or in full beta-adrenergic receptor blockers.

In the same manner, the blockade of beta receptors as well as alpha-1 receptors works in reducing blood pressure.

Enter yohimbine.

Chemically, yohimbine is classified as an alpha-2 adrenergic receptor blocker. Alpha-2 adrenergic receptors are located primarily in the abdominal and pelvic area, including the primary sex organs.

As a receptor blocker, yohimbine is, in a way, an anti-hormone. But in another way, it is similar to cocaine and amphetamine in causing mental agility and arousal.

Why?

The only explanation that seems to make sense is that by interfering with the docking of epinephrine (adrenaline) in the abdominal and pelvic tissue, or by even replacing it from alpha-2 receptors to which it normally is bound, yohimbine causes an increase of freely circulating epinephrine / adrenaline.

The freely circulating additional epinephrine (adrenaline) as a hormone exerts the typical adrenergic effect on the heart, leading to

an increased heart rate (tachycardia, palpitations), which will always occur with a sufficiently high dosage of yohimbine. But because epinephrine is not just a hormone, but also a neurotransmitter, it also affects the central nervous system in a manner that actually is quite similar to cocaine or amphetamine, with increased alertness, mental agitation, and proneness to arousal, sexual and otherwise.

Yohimbine is unique in that it has a dual aphrodisiac function: it improves sexual function by displacing hormonal epinephrine from alpha-2 adrenergic receptors in the pelvic area, and it increases proneness to arousal through supplying the epinephrine from the alpha-2 adrenergic receptors to the central nervous system (the brain), where it is active as a neurotransmitter.

As a pro-sexual drug, yohimbine has a definite edge over cocaine, amphetamine, and methamphetamine. The three street drugs may have the effect of causing sexual arousal, but at the same time interfere negatively with sexual function.

This is the case because hormonal epinephrine not only has the function to increase heart rate and blood pressure in order to make the body ready for fight or flight, but also to shut down functions that are not essential for fighting or fleeing. Blood is drawn from the digestive tract while bowel movement may be hastened to rid the body of weight.

Vasodilatation in the genital tract is made impossible. An erection during a fight would be an unwelcome obstacle, and a highly vulnerable target on top of that. This is why the increased catecholamine levels effected by cocaine, amphetamine, and methamphetamine all lead to a strong shrinkage of the male genitals. Therefore, what one gets from cocaine and amphetamines is a plus in desire and a minus in capability. an odd combination indeed.

Yohimbine, on the other hand, does not elevate epinephrine effects throughout the body. Yohimbine effects a minus of epinephrine in the abdominal and genital areas where alpha-2 adrenergic receptors prevail, and a plus of epinephrine in the central nervous system and other, mostly upper parts, of the human body.

In order to understand why the interference with alpha-2 adrenergic

receptors works to facilitate erections, one has to know that the normal, flaccid genital state is, in the first place, only caused by hormonal epinephrine (adrenaline) being almost permanently docked to alpha-2 adrenergic receptors. To achieve an erection normally, nerve impulses will have to initiate a physiological process by which epinephrine (adrenaline) is removed from alpha-2 adrenergic receptors.

The same effect can be reached by ingesting some 5 to 50 milligram of yohimbine.