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Drugs & Chemicals Intro & Tutorial

Part 1: Introduction and Indigenous chemicals (neurotransmitters & hormones)

Introduction

A ‘drug’ is usually thought of by most people as either a ‘medicine’ that comes with a doctor’s prescription, or something illegal purchased on street corners from unscrupulous persons with suspicious haircuts, but we have to go beyond such stereotypes here and try to make a chemist out of you. (If you’re a chemist already, it’s okay to have a suspicious haircut).

In neurohacking, we tend to think of all chemical substances including drugs and nutrients as exactly what they are –chemicals.

All substances are potential drugs, in the chemistry sense. Sugar or salt can have just as profound an effect on the human brain and body as aspirin or sleeping tablets, and all substances, ingested or produced inside the body, have some kind of an effect.

It is wise to remember that many substances that are essential nutrients or life saving medicines can also be deadly poisons in higher doses. Plants were humankind’s first medicines as well as foods, and many drugs today are still made from plants. Sugar and salt are used to treat dehydration in many tropical gastro-intestinal diseases, but a pint of salt water on an empty stomach could well kill you. No chemical substance is ‘good’ or ‘bad’ in itself; its benefit or harm depends on how we use it. Heroin has saved many an injured person from death through shock, and many prescription drugs taken exactly as directed have killed people via ‘side effects’. These days, hormones and even neurotransmitters are used as drugs, both in the

medicinal and the recreational sense.

Thus we approach ‘chemicals’ in a purely scientific sense, because if you can get into that habit of thinking, your awareness of what you are putting into yourself and what the consequences are likely to be will be that much more astute. Herbs, drugs, vitamins, supplements and even food; we don’t make a distinction here because biology doesn’t –it will treat all things entering your body as exactly what they are.

Alcohol, tobacco, cannabis, caffeine and prescription medicines are all subject to different laws or rules in different countries. In some countries certain substances are illegal and you should find out what the laws are where you live. It may also be illegal in some countries to import or export herbs, plants and seeds and some herbal remedies. Some social groups such as Mormons or Vegans also strongly discourage or ban some substances and you should be careful not to offend.

You are probably using some substances to augment your brain’s performance in some areas already [for example coffee, alcohol, sugar, nicotine]. The common sense rule for working with chemicals is to always try to find the gentlest, safest, most effective product.

You should remember that for many others, drug companies included, the rule for working with chemicals is to find the most profitable product; not the safest or the most effective. On top of that, a big problem with chemicals is adulteration. This happens with prescription drugs, supplements and vitamins which can have all kinds of extra ingredients that might not be good for you. Supposedly authentic medications bought online can turn out to be simply colored chalk. Adulteration also happens in food and drink, and if you suffer from allergies and/or mood swings, this is one of the first places to look.

Much of the media will tell you a load of nonsense about what drugs are actually dangerous.

Here is a graph of some of the most dangerous substances commonly in use, measured by how many people die using them and how much permanent damage they can cause:

Some of these results may surprise you. What may surprise you more is that sugar and junk food would, if they were included, be right up there in front of heroin and cocaine (they cause a lot more deaths and permanent damage than any of these). So take your propaganda with a pinch of salt (or preferably without, as table salt is pretty dangerous as well).

There are three parts in this tutorial:

1. Indigenous chemicals [the natural chemicals inside your brain, e.g., neurotransmitters, messengers and hormones]. Most chemicals that affect the brain work by affecting neurotransmitters, so understanding our own internal chemicals helps us to see how drugs work.
2. Synthetic introduced chemicals [drugs, e.g. medications, recreational drugs (manufactured), 'smart' drugs, food additives]
3. 'Natural' introduced chemicals [e.g. caffeine, sugar, foods, recreational drugs (botanical), herbs, supplements]

The tutorial concludes with some articles about drugs and drug use.

Part 1 – Indigenous chemicals

(It is useful to know some basic anatomy & physiology before studying neurotransmitters.)

Neurotransmitters

If you've done the Intal tutorials, you'll remember than neurons pass their signals across a synaptic cleft, or gap between brain cells, in a chemical fashion, and that this causes the neuron to fire an electrical 'spike'. Thus, information in the form of electrical action potentials in a neuron is able to pass along to the neuron next to it, via the release of these chemicals migrating across the tiny gap between the cells. (On attaching to receptors at the second cell the neurotransmitter influences the second cell's activity.)

The principle sources of neurotransmitters are our brain cells themselves, but they are moderated by the hypothalamus and pituitary gland in the brain.

This system is called the HPA (hypothalamic-pituitary-adrenal) axis.

The main indigenous chemicals we are concerned with in n-hacking are:

- Acetylcholine

- Cortisol
- Dopamine
- Endorphins
- Noradrenalin [norepinephrine]
- Oxytocin
- Serotonin

Acetylcholine (ACh)

Is made in the basal forebrain and in the brainstem.

Acetylcholine has functions both in the peripheral nervous system (PNS) and in the central nervous system (CNS) as a neuromodulator, responsible for timing and regulation of processes.

In the central nervous system, ACh is involved with synaptic plasticity, specifically in learning and short term memory, mediates arousal and reward, has an important role in the enhancement of sensory perceptions when we wake up, and is important in sustaining our alertness and attention.

Learning & plasticity:

Acetylcholine has been shown to enhance the amplitude of synaptic potentials following long term potentiation (LTP) in many regions.

Attention

In the cerebral cortex, ACh filters out weak sensory inputs and amplifies inputs that we focus on. These effects of ACh function to improve the signal noise ratio of cortical processing.

Things that increase acetylcholine

There are two main classes of acetylcholine receptor (AChR), nicotinic and muscarinic.

Nicotinic AChRs are stimulated by nicotine and acetylcholine. They are of two main types, muscle type and neuronal type. The former can be selectively blocked by curare and the latter by hexamethonium.

Muscarinic receptors are stimulated by muscarine and acetylcholine, and blocked by atropine (extracts from the plant deadly nightshade).

Since a shortage of acetylcholine in the brain has been associated with Alzheimer's disease, some drugs that inhibit acetylcholinesterase (the enzyme that destroys ACh) are used in the treatment of that disease.

Direct acting

-

Acetylcholine (all receptors)

-

Bethanechol (M receptors)

-

Carbachol (M receptors plus some N receptors)

-

Methacholine (M receptors)

-

Cevimeline

-

Pilocarpine (M receptors)

-

Muscarine (M receptors)

-

Suberylcholine

-

Arecholine

-

Nicotine (in small doses)

-

Acetyl l-carnitine

Acetylcholinesterase inhibitors

Enzyme inhibitors increase the action of acetylcholine by delaying its degradation; some powerful ones have been used as nerve agents (Sarin & VX gas). In clinical use, they are administered to reverse the action of muscle relaxants, and to delay symptoms of Alzheimer's disease (e.g., Rivastigmine, which increases cholinergic activity in the brain).

Reversible:

- Donepezil
- Edrophonium
- Galantamine
- Neostigmine
- Norepinephrine
- Physostigmine
- Pyridostigmine
- Rivastigmine
- Tacrine
- Huperzine A

Physostigmine is one of a few drugs that are used as antidotes for anticholinergic poisoning. Nicotine also counteracts anticholinergics.

Irreversible or semi-permanent:

- Echothiophate
- Isofluorophate
- Organaphosphate insecticides (eg Malathion etc)
- Organaphosphate nerve agents (eg Sarin gas etc)

Many poisons work by upsetting Acetylcholine. Mercury causes dysfunction of the enzyme choline acetyltransferase. This inhibition may lead to acetylcholine deficiency, and can have consequences on motor function. Botulin acts by suppressing the release of acetylcholine; where the venom from a black widow spider has the reverse effect.

ACh release-promoters

- Cisapride
- Metoclopramide

Things that decrease acetylcholine

The majority of anticholinergic drugs are antimuscarinics. Antinicotinic drugs are used as skeletal muscle relaxants in surgical use, along with a few of the depolarising agents and drugs of other categories structurally related to curare.

Examples: ipratropium bromide (Atrovent), oxitropium bromide (Oxivent), Tiotropium (Spiriva).

Cortisol

The pituitary gland prompts the release of cortisol from the adrenal medulla through the action

of ACTH, a hormone produced in the pituitary gland. ACTH itself is secreted due to the action of CRH (corticotropin-releasing hormone) produced by the hypothalamus (hence the HPA axis!). Normally, cortisol levels are highest in the early morning. They fall to their lowest level 3-5 hours after the onset of sleep.

In normal release, cortisol has widespread actions which help us respond to danger and maintain homeostasis. Over-production of cortisol occurs in anxiety (chronic stress).

Excess Cortisol is related to:

- Diabetes
- It counteracts insulin, contributing to hyperglycemia.
- Skin Aging
- Loss of collagen from skin, caused by cortisol, is ten times greater than loss from any other tissue.
- Gastric secretion
- Cortisol stimulates gastric acid secretion.
- Sodium
- Cortisol inhibits loss of sodium
- Potassium
- Sodium load augments the intense potassium excretion by cortisol
- Water
- Cortisol also acts as an anti-diuretic hormone. Half the intestinal diuresis is so controlled.

- Copper
- Many copper enzymes are stimulated to an extent which is often 50% of their total potential by cortisol.
- Immune system
- Cortisol can weaken the activity of the immune system, as it prevents proliferation of T-cells.
- Bone metabolism
- It lowers bone formation thus favoring development of osteoporosis in the long term.
- Shock response
- Cortisol moves potassium out of cells in exchange for an equal number of sodium ions. This can cause a major problem with the hyperkalemia of metabolic shock from surgery.

- Calcium
- Cortisol reduces calcium absorption in the intestine.
- Memory
- In healthy amounts, cortisol cooperates with norepinephrine to weight short-term

emotional memories; this may originate as a means to remember what to avoid in the future. However, long-term exposure to cortisol results in damage to cells in the hippocampus. This damage results in impaired learning and memory.

- Additional effects
- Cortisol increases blood pressure and reduces serotonin levels in the brain

Factors generally reducing cortisol levels

-

Magnesium supplementation decreases serum cortisol levels after aerobic exercise, but not in resistance training.

-

Omega 3 fatty acids can lower cortisol release influenced by mental stress

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Music can reduce cortisol levels in certain situations

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Massage and cuddling can reduce cortisol.

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A low GI diet helps maintain healthy cortisol levels.

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Laughing and the experience of humour can lower cortisol levels.

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Soy derived Phosphatidylserine interacts with cortisol but the right dosage is still unclear.

-

Meditation and mindfulness exercises reduce cortisol levels.

-

The relaxation response balances cortisol to healthy levels.

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Being in a natural environment reduces cortisol production.

-

Serotonin, endorphins, anandamide, cannabinol, opioids and oxytocin can all reduce cortisol production .

-

Vitamin C may slightly blunt cortisol release in response to a mental stressor.

-

Black tea may speed up recovery from a high cortisol condition

Factors generally increasing cortisol levels

-

Sleep deprivation and unnatural awakening (eg with alarm clocks) increases cortisol levels.

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Intense or prolonged physical exercise stimulates cortisol release in order to maintain blood glucose. Proper nutrition and high-level conditioning can help stabilize exercise-related cortisol release.

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Burnout is associated with higher cortisol levels.

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Feeling unsafe, enslaved or coerced increases cortiol levels.

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Traumatic or constant stressful events elevate cortisol levels in the blood for prolonged periods. These events may be conscious or unconscious.

-

Subcutaneous adipose tissue (fat storing tissue) regenerates cortisol from cortisone

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Some oral contraceptives increase cortisol levels in young women who perform whole-body resistance exercise training.

-

Commuting increases cortisol levels, related to the length of the trip, the amount of effort involved and the predictability of the trip

-

Vitamin deficiency and poor nutrition can increase cortisol levels

Dopamine (DA)

Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area. Dopamine is also a neurohormone released by thehypothalamus..

Dopamine has roles in motor functions, the motivation and good mood we experience from desire, attention and focus and spatial memory. Dopamine is believed to provide a teaching signal to parts of the brain responsible for acquiring new behavior.

It has many functions in the brain, including important roles in behavior and attention, voluntary movement, motivation, sleep, mood, memory and learning.

We need dopamine to make norepinephrine.

Most articles about dopamine will tell you that it controls the ‘reward system’ in humans. This is not true, and is a good example of the ‘mainstream’ being somewhat out of date. It’s now known that dopamine controls the desire, motivation and orientation part of learning; serotonin and endorphins provide the ‘reward’.

Badly out of date publications will tell you that dopamine controls the ‘pleasure system’. In fact, all neurotransmitters contribute to pleasure in different ways (desire is pleasant, certainly, but so is fulfilment!).

Things that increase dopamine

- Dopamine can be supplied as a drug that acts on the sympathetic nervous system (SNS), increasing heart rate and blood pressure. To treat Parkinson's disease, a precursor of dopamine; L-DOPA is given because it can cross the blood-brain barrier.
- Intropin is dopamine administered outside the CNS (cannot normally cross the blood-brain barrier).
- Dopamine is released by following up desires for food, sex, drugs, or new learning experiences.
- Drugs such as cocaine, alcohol, nicotine, heroin, morphine, methylphenidate and amphetamines lead to an increase of dopamine.
- Other drugs that increase dopamine include: Parlodel (bromocriptine), Dostinex (cabergoline), Permax (pergolide), Mirapex (pramipexole), Requip (ropinirole), Apokyn (apomorphine), Neupro (rotigotine).
- Sustained-release bupropion is marketed as an antidepressant and as an aid to smoking cessation. It inhibits norepinephrine and dopamine reuptake (eg it increases dopamine).

- There is some recent evidence implying that SNRIs may also increase dopamine transmission

Libido can be increased by drugs that affect dopamine.

Abnormally high dopamine transmission has been linked to paranoia, psychosis and schizophrenia, as well as manic behavior.

Things that reduce dopamine

- Neuroleptics/antipsychotics reduce dopamine activity. They have been shown to reduce motivation, cause anhedon (inability to experience pleasure), and long-term use has been associated with irreversible movement disorder. Deficient dopamine neurotransmission is implicated in ADHD.
- A lot of drugs reduce dopamine; too many to list here. Among them are Monoamine

oxidase (MAO), Reserpine, clozapine, risperidone, olanzapine, quietapine, ziprasidone, metoclopramide, droperidol, domperidone, amoxapine.

- Serotonin modulates dopamine.

Drugs that adjust dopamine levels in the brain greatly affect attitudes of optimism or pessimism and how people respond to what they see as successes or failures.

Endorphins

The naturally occurring endorphins are produced by pro-hormones. Beta-endorphin is made in the pituitary. Methionine and Leucine enkephalins are made in the adrenal medulla.

Produced by the pituitary gland they have pain killing properties and impart a feeling of well-being. Endorphins work as "natural pain relievers." Immediately after injury, endorphins allow humans to feel a sense of power and control over themselves that allows them to persist with activity for an extended time.

These abilities make possible our adaptation to the environment. The feeling of analgesia has proved to be extremely advantageous toward survival. Endorphins ensure that survival comes first, and recuperation comes later. This is an evolutionary advantage for species who have developed a degree of pain control in times of stress.

Endorphins emphasize our feelings of belonging and togetherness, and a shortage leads to feelings of separation, isolation and alienation.

Things that increase endorphins

- Strenuous exercise, excitement, pain, spicy food, orgasms.
- Capsaicin (the active chemical in red chili peppers) also has been shown to stimulate endorphin release.
- In 2003, clinical researchers reported that profound relaxation in a REST chamber or float tank triggers the production of endorphins.
- The pain-killing and pleasurable effects of morphine, the narcotic drug derived from the opium poppy, is widely known. Endorphins and enkephalins are chemicals that bear a surprising similarity to morphine. It is interesting to note that the term "endorphin" is a contraction of "endogenous morphine" (that is, morphine formed within the body). Thus, the discovery of endorphins followed the realization that certain regions of the brain bound opiate drugs with high affinity.
- Natural opiates, primarily morphine, codeine and thebaine.
- Kratom (leaves of Mitragyna Speciosa)
- Salvinorin A (Salvia Divinorum)
- Corydalis (contains the alkaloid bulbocapnine)
- Semi-synthetic opioids: created from the natural opiates, such as hydromorphone, hydrocodone, oxycodone, oxymorphone, desomorphine, diacetylmorphine (heroin), nicomorphine, dipropanoylmorphine, benzylmorphine, ethylmorphine.
- Fully synthetic opioids: such as fentanyl, pethidine, methadone, tramadol, dextropropoxyphene.

Things that decrease endorphins

- Naloxone and naltrexone are commonly used opioid antagonist drugs which bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This effectively blocks the receptor, preventing the body from responding to opiates and endorphins.

- Cortisol decreases endorphin release.

Noradrenalin [norepinephrine]

Made in an area of the brain stem called the locus ceruleus, and the lateral tegmental field.

The primary neurotransmitter in the peripheral sympathetic branch of the autonomic nervous system. It is also produced in the adrenal medulla. In the brain, norepinephrine functions as an excitatory neurotransmitter, responsible for our drive, ambition, alertness, focus and long-term memory (learning). The effects are alertness and arousal.

Norepinephrine is used medically for attention-deficit/hyperactivity disorder (ADHD), depression and hypotension. Norepinephrine itself cannot cross the blood-brain barrier, so drugs such as amphetamines are necessary to increase brain levels.

Norepinephrine is mainly used to treat patients in vasodilatory shock states such as septic shock and neurogenic shock, and is also used as a vasopressor medication (eg Levophed) for patients with critical hypotension.

Epinephrine is produced from norepinephrine enzymatically, in both the brain and adrenal glands. Only small amounts of epinephrine are produced in the brain, relative to the more common norepinephrine, however, adrenal epinephrine is the powerfully active, main stress hormone. Strong cardiac stimulation: raising the heart rate and contraction strength.

Things that increase norepinephrine

Norepinephrine, along with dopamine, has come to be recognized as playing a large role in attention and focus. For people with ADHD, psychostimulant medications such as methylphenidate (Ritalin/Concerta), dextroamphetamine (Dexedrine), and adderall (a mixture of dextroamphetamine and racemic amphetamine salts) are prescribed to help increase levels of norepinephrine and dopamine.

- Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor, and is a unique ADHD medication, as it affects only norepinephrine, rather than dopamine. However, it may not be as effective as the psychostimulants are with many people who have ADHD. Other SNRIs, currently approved as antidepressants, have also been used for treatment of ADHD.)
- SNRIs (serotonin-norepinephrine reuptake inhibitors) are antidepressants that treat depression by increasing serotonin and norepinephrine.

- Nortriptyline and Doxepin, tricyclic antidepressants (TCAs) increase norepinephrine activity.
- Alpha- and beta-adrenergic agonists, amphetamines, tyramine, ephedrine and pseudo-ephedrine all increase norepinephrine.

Things that decrease norepinephrine

- Acetylcholine modulates norepinephrine.
- Clonidine decreases release of norepinephrine
- Alpha- and Beta-blockers reduce norepinephrine

Oxytocin

Oxytocin is made in the hypothalamus and stored in the pituitary gland. Oxytocin is also made by some neurons in the paraventricular nucleus that project to other parts of the brain and to the spinal cord.

The structure of oxytocin is very similar to that of vasopressin. Oxytocin and vasopressin are the only known hormones released by the human posterior pituitary gland to act at a distance.

Recent studies have begun to investigate oxytocin's role in various behaviors, including sexual arousal and orgasm, social recognition, receptivity, bonding, anxiety reduction, generosity, empathy increase, trust, love, and maternal behaviors. Oxytocin evokes feelings of friendliness, reductions in anxiety, and feelings of calmness and security around a mate. Many studies have already shown a correlation of oxytocin with social bonding, increases in trust, and decreases in

anxiety. One study confirmed that there was a positive correlation between oxytocin plasma levels and an anxiety scale in adult bonding. This suggests that oxytocin may be important for the inhibition of anxiety.

Under certain circumstances oxytocin indirectly inhibits release of cortisol.

Low oxytocin may play a role in autism and oxytocin may be an effective treatment for autism’s 's repetitive and affiliative behaviors. Oxytocin treatments also result in an increased retention of affective speech in adults with autism. Two related studies in adults, in 2003 and 2007, found that oxytocin decreased repetitive behaviors and improved interpretation of emotions.

Experimental subjects given nasally administered oxytocin displayed "the highest level of trust" twice as often as the control group. Nasally administered oxytocin has also been reported to reduce anxiety, possibly by inhibiting the amygdala.

According to some studies, oxytocin inhibits the development of tolerance to various addictive drugs (opiates, cocaine, alcohol) and reduces withdrawal symptoms.

Some have suggested that the trust-inducing property of oxytocin might help those who suffer from social anxiety and mood disorders, while others have noted the potential for abuse with scams (confidence tricks) and military applications.

Things that increase oxytocin

- Oxytocin is sold as Pitocin, Syntocinon, and similar peptides Demoxytocin and Carbotecin.
- Serotonin can increase oxytocin
- MDMA (ecstasy) increases feelings of love, empathy and connection to others by stimulating oxytocin activity via activation of serotonin.
- Compound 39

Things that reduce oxytocin

- Cortisol
- Atosiban (tractocile) reduces oxytocin
- Lots of new synthetics, with names like GSK-221,149 and L-368,899 (CAS# 148927-60-0) and WAY-162,720
- Anything reducing oxytocin will almost always reduce vasopressin as well.

Serotonin (5-HT)

Is made by a series of cell groups in the brainstem collectively known as the Raphe nuclei. It is only these neurons that can make serotonin.

Many normal behaviors depend of intact serotonin function in the brain. Its function is primarily inhibitory, working with GABA to prevent over-excitation.

Serotonin has various roles, including the regulation of mood, appetite, resource management, self esteem and confidence, sleep, muscle contraction, memory and learning, and immunity.

Behaviorally it tends to reduce movement, slowing animals down, relaxing them, increasing the amount of time they spend (for example) in the presence of food, and activating the muscles used for feeding & digestion. Together with norepinephrine it optimises behavior to match resources, and depletion of these transmitters cues overeating behavior that is typical of a low-food environment, while the opposite occurs if serotonin is increased.

Serotonin is necessary for normal mating behavior, and the inclination to leave food to search for a mate, spend enough time with a mate to reproduce, return to a safe shelter for birthing, and hygienically care for self and young.

It is our warning transmitter for avoiding toxins and prompts feelings of disgust that make us avoid dangerous substances and can produce the contractions necessary for vomiting in case of poisoning.

It affects insulin and blood sugar levels (depletion leads to obesity and arrested development), suppressing insulin release from the pancreas, and modulating fetal growth.

Serotonin can also act as a growth & repair factor directly in the liver and in bones.

It is also involved in self esteem, confidence and the perception of social rank. Epigenetics in the form of social experience alters the proportion between different serotonin receptors that have opposing effects on the “fight or flight” response, strongly affecting which option an animal is likely to choose. Serotonin inhibits the fleeing reaction in subordinates, but enhances it in socially dominant or isolated individuals. The more serotonin we have, the more confident and less aggressive we are, (although violent behavior is still used in self defense.) Very low serotonin correlates strongly with feelings of hopelessness and suicide.

Serotonin works well as an anxiolytic and increases patience and tolerance.

Immunity: In the blood, the major storage site of serotonin is platelets. Bleeding causes serotonin release, which constricts blood vessels and allows the blood to clot, preventing further loss of blood and also infection.

Activation of the 5-HT2A receptor with DOI (see below) produces superpotent anti-inflammatory effecs in cardiovascular related tissues, as well as potent anti-inflammatory effects in non-cardiovascular tissues. Other 5-HT2A agonists like LSD also have potent anti-inflammatory

effects.

Things that increase serotonin

- Fluoxetine (Prozac) and other related compounds exert their therapeutic effect on depression and obsessive compulsive disorder (OCD) by acting on serotonin in the brain.

- Hallucinogenic drugs such as LSD, mescaline, psilocin, DOI (2,5-Dimethoxy-4-iodoamphetamine), DMT, TCB-2, Br-DFLY and 2C-B target serotonin sensitive cells by selectively mimicking some of the effects of serotonin.
- Soil bacteria contain serotonin which can be absorbed through the skin
- Fungi, plants, fruit and vegetables contain serotonin
- Several classes of drugs target the 5-HT system including some antidepressants, antipsychotics, anxiolytics, psychedelic drugs and empathogens.
- SSRIs (Selective Serotonin Reuptake Inhibitors) increase serotonin.
- SNRIs (serotonin-norepinephrine reuptake inhibitors) are antidepressants that treat depression by increasing serotonin and norepinephrine.
- Nortriptyline and Doxepin, tricyclic antidepressants (TCAs) increase serotonin activity, but tend to produce unwanted side effects due to the nonspecific activation of histamine, acetylcholine and adrenergic receptors. For this reason, they have largely been replaced by newer selective reuptake drugs such as fluoxetine (Prozac).
- Clomipramine and paroxetine increase serotonin.
- Azapirones (eg Buspirone, Gepirone, Tandospirone) increase serotonin.

Things that reduce serotonin

- Cortisol and dopamine reduce serotonin
- Too much cannabis (due to consistently high dopamine)
- Ergot alkaloids and a few ergot derivatives such as metergoline.
- Ketanserin, ritanserin (partially)
- Nefazodone, Pizotifen
- Atypical antipsychotics (eg clozapine, olanzapine, quietapine, risperidone)
- MDL-100,907 (prototype of another new series of 5-HT2Aantagonists) and cyproheptadine

- AMDA and related derivatives are selective 5-HT2A antagonists.
- AC-90179 potent and selective inverse agonist at 5-HT2A, also 5-HT2C antagonist.
- Eplivanserin -a new sleeping pill under development, acts as a selective 5-HT2A inverse agonist.
- Pimavanserin (ACP-103) orally active, antipsychotic, now in human clinical trials.

Other neurotransmitters you will study as you continue to progress are:

- Anandamide
- ACTH [Adrenocorticotrophic hormone]
- DHEA-S
- GABA [Gamma amino butyric acid]
- Glutamate
- Melatonin
- NMDA [n-methyl d-aspartate]
- Vasopressin

We only give details of some of these below. If you wish to learn more, look up the individual chemicals and do the tutorials.

DHEA-S is the most abundant hormone in the human body. It is synthesized from cholesterol in the adrenals, gonads, fat, skin, and brain. It is the precursor of androstenedione, testosterone, and estrogen. DHEA-S is the stable form found in blood and saliva. DHEA-S is inversely related to cortisol. A shift in this ratio toward higher cortisol may indicate increasing adrenal fatigue in the face of chronic stressors. Depletion in both adrenal hormones is indicative of adrenal exhaustion and a failed ability to deal with stress.

GABA: (Gamma Amino Butyric Acid) is the most important and widespread inhibitory neurotransmitter in the brain. Its main job is to inhibit the brain's most common excitatory

neurotransmitters norepinephrine, epinephrine, and glutamate. Glutamate: is the most common excitatory neurotransmitter in the CNS, exerting powerful stimulatory effects on neuronal tissue. It is also normally involved in learning and memory. Excess glutamate is dangerous to nervous tissue, causing excitotoxicity, neuron damage and death.

Polarity in Neurotransmitters

There is a natural polarity in all animal behavior and all neurotransmission.

Neurochemistry is the link between concrete, material, physical behavior, emotion, and cognitive thought –the link between biology and psychology; between what we need and the behavior necessary to achieve it. It's now known that our neurochemical state affects what kinds of thoughts we can access from memory as well as our outward behavior. If you think about this, you can see what a huge impact on our personality overall neurotransmitters really have!

Lest we forget, and as much as some might wish to deny, we are animals. Mammals to be more precise; higher primates to be even more precise, but animals nevertheless.

All animal behavior is based at root on the polarity of stress/relaxation, communicated chemically by neurotransmitters and modulated by feedback. To synchronize brain, body & mind, the hypothalamus links the brain and nervous system to the endocrine (hormone) system via the pituitary gland. Biology uses 6 main basic types of behavior to achieve all its needs, and these show clear polarities of function.

relaxation

stretching

Serotonin: self care & hygiene (“serene & clean”)

Dopamine: Seeking & warning (“seek & squeak”)

Acetylcholine: interaction & construction (“create & cooperate”)

Norepinephrine: resource assessment, gathering & self presentation (“assess & impress”)

Endorphins: judgement, problem solving & decision making (“enjoy & deploy”)

Oxytocin: alliance-making (“befriend & bond”) or Cortisol: defense (“fight or flight”)

These basic behaviors are normally instinctive. Hopefully you can see how drives such as sex and hunger use “seeking” behavior (courting and hunting respectively, even if these days hunting means looking for the best pizza online) and how 'construction behavior' can apply equally to nest building, little wooden huts and the international space station. Fact is, ALL of our behaviors relate back to one or more of these essential 'behavior templates' for different types of interaction, and each pair of neurotransmitters is based on the stress-relaxation polarity.

If you want to learn more about neurotransmitters, we suggest you do the main neurohacking tutorials. We mention them here because neurotransmitters, hormones, and synthetic analogs of both are often used as medication in various disorders or for recreational purposes. Many drugs work by affecting the rate and quantity of neurotransmitters released and the speed at which they are broken down and reabsorbed.

Hormones and the Endocrine System

The endocrine system consists of the hormones of the body, their sites of release and their sites of action. A hormone is a substance that is secreted into the blood at one location and transported in the blood to another location, where it exerts its effect on a target organ. The principle sources of hormones are the various glands that are situated throughout the body, but they are controlled by the hypothalamus and pituitary gland in the brain.

For example, testosterone is released by the testes and adrenal glands and circulates in the bloodstream. It has effects at the male genitalia, in the developing fetus, and in the brain. Another hormone, arginine vasopressin, is secreted from a gland located at the base of the brain, the pituitary gland, in response to dehydration. It is transported in the blood to the kidney, where it slows up the production of urine. If the body is overhydrated, secretion of the hormone is slowed or stopped altogether and the excretion rate of water is high. In this way, regulation of the body water level is maintained.

Via the brain, hormones both influence behavior and are influenced by it. Thus, for example, a certain hormone influences the activity of parts of the brain controlling fear and thereby affects

behavior. Reciprocally, the brain influences the secretion of hormones. By its effects on the brain, the environment can influence levels of hormones.

“Spectacular growth of the field of neuroendocrinology offers the present generation of neurobiologists unparalleled opportunities to explore with great sophistication the influence of neural activity on endocrine secretion and the effect of hormones, in turn, on neural activity and behavior.” - Bruce S. McEwen, Laboratory of Neuroendocrinology, Rockefeller University

Using Synthetic Hormones

Many hormones are neuroactive (some are also neurotransmitters!) It is important to remember that hormones themselves do not cause behaviors; rather, hormones induce chemical changes in particular sets of neurons, making certain behavioral outcomes more likely as a result of the strengthening or weakening of particular neural pathways.

The two most popular types of synthetic hormones are contraceptives and anabolic steroids/growth factors.

The brain has both estrogen and progesterone receptors. In women who have epilepsy, seizures are known to occur more frequently during times of high estrogen (late follicular phase and ovulation) and they are decreased when progesterone is high. In this sense, progesterone acts a a brain anesthetic to some degree. High doses of progesterone can be very sedating.

Women who have depression, have lower brain levels of serotonin, thus the success of medications that block the body's degradation of serotonin and allow brain levels to remain higher. Estrogens are known to block one of the enzymes (monoamine oxidase - MAO) which degrades serotonin with the result of elevating mood. Progestogens, probably more so than natural progesterone, increase MAO concentration thus producing depression and irritability. Pure progestogen without estrogen, such as DepoProvera is know to worsen depression in

women who already have a tendency toward or clinical signs of depression. The combination of estrogen plus progestogens such as used in birth control pills and menopausal hormonal replacement therapy does not tend to worsen mood because the compounds are neutralizing each other. There are some women who are more sensitive to certain hormones so their doses may need to be adjusted.

Anabolic steroids are artificial versions of a hormone that's in all of us -- testosterone. (That's right, testosterone is in girls as well as guys.) Testosterone not only brings out male sexual traits, it also causes muscles to grow.

Some people take anabolic steroid pills or injections to try to build muscle faster. ("Anabolic" means growing or building.) But steroids also have other effects. They can cause changes in the brain and body that increase risks for illness and they may affect moods.

Anabolic steroids have been shown to impair learning and memory. They can also lead to changes in mood, such as feelings of depression or irritability. If neurotransmitters are already out of balance, steroids can trigger really aggressive behavior.

Anabolic steroids can change the messages the hypothalamus sends to the body. This can disrupt normal hormone function. In guys, they can interfere with the normal production of testosterone. They can also act directly on the testes and cause them to shrink. This can result in a lower sperm count and reproductive ability. (They can also cause an irreversible loss of scalp hair.)

In girls, anabolic steroids can cause a loss of the monthly period by acting on both the hypothalamus and reproductive organs. Testosterone has a definite libido, response, and orgasmic facilitation effect on women. Numerous companies are currently testing gels and transdermal patches, but none are anywhere near approval. T-supplementation for females is controversial and may have side effects such as clitoral enlargement, hirsutism, loss of scalp hair, deepening of the voice, and acne. Many of these changes are (currently) irreversible.

E3 (estrone)

A topical creme for antiaging and antiacnegenic activity. This can currently be compounded at the 1% concentration for the eradication of photoaging and to ameliorate the effects of testosterone supplementation on the face, without systemic effects.