Serotonin and Dopamine: A Primer

The Molecules of Reward

Serotonin and dopamine are part of a group of compounds called biogenic amines. In addition to serotonin and dopamine, the amines include noradrenaline, acetylcholine, and histamine. This class of chemical messengers is produced, in turn, from basic amino acids like tyrosine, tryptophan, and choline. The amines are of great interest, because both mood-altering drugs and addictive drugs show a very straightforward affinity for receptors sites designed for endogenous amines.

Addictive drugs have molecules that are the right shape for the amine receptors. Drugs like LSD and Ecstasy target serotonin systems. Serotonin systems control feeding and sleeping behaviors in living creatures from slugs to chimps. Serotonin, also known as 5-HT, occurs in nuts, fruit, and snake venom. It is found in the intestinal walls, large blood vessels, and the central nervous system of most vertebrates. The body normally synthesizes 5-hydroxytryptamine, as serotonin is formally known, from tryptophan in the diet.

Thus far, no other substance found the central nervous system has as many diverse receptor actions as 5-HT. The average adult has only about 10 milligrams of serotonin in his or her body. It is involved, to one degree or another, in appetite, sleep, mood, memory, learning, endocrine regulation, smooth muscle contractions, migraine headaches, motility of the GI tract, blood platelet homeostasis, so on. Serotonin also plays a large role in initiating and shaping certain kinds of behavior, especially behaviors of a sexual or hallucinatory nature. In animal models, lower serotonin levels correlate with higher levels of violence.

A receptor-selective agent like Sumatriptan, a popular migraine medication, works by binding selectively to a serotonin receptor subtype involved in arterial circulation and dilation. The difference between serotonin-active drugs like sumatriptan, and similarly serotonin-active drugs LSD or Ecstasy, is that the former locks exclusively into these “5-HT1” receptors, and nowhere else. The ergot alkaloids are all over the serotonin system, causing general surges of their own.
Psychedelic drugs like LSD and Ecstasy (chemically known as indoleamines) and
mescaline (phenethylamines) make up the two major classes of hallucinatory drugs. They are both partial agonists at 5-HT receptors, boosting serotonin particularly in the cerebral cortex and the locus coeruleus. There is also some enhancement of glutamine activity as well. Other 5-HT agonists, like ondansetron (trade name Zofran), do not have that effect. Ondansetron helps block the nausea of chemotherapy by blocking serotonin activity in the GI tract. Vomiting is a serotonin-mediated reflex. In this case, it is the 5-HT3 receptor subtype that is of note. Ondansetron’s selective affinity for that subtype makes it a useful anti-emetic.

Dopamine, like serotonin appears to be strongly involved in mediating craving--drug hunger, as well as real hunger. This yields a partial answer to one of addiction’s mysteries: Why would a drug addict, an alcoholic, continue to use when the adverse effects of continued use have long ago swamped whatever euphoric sense of well being, or even just plain normalcy, that once was obtained through the drug? One answer might be that dopamine causes human beings to pay attention to stimuli that are potentially rewarding. Even in the absence of any possibility of reward--on a desert island, in a rehab clinic--dopamine dysregulation could kindle episodes of fierce craving, because such episodes had led in the past to a renewed ingestion of the drug in question--all the fiercer, these cravings, this drug hunger, whenever the addict was exposed to direct cues, like seeing the drug, or being in places where the addict had used before.

Scientists have managed to record a rise in dopamine levels in lab rats simply by cueing the rats to anticipate a pleasurable event--food, sex, sweet drinks. For example, you could condition the rats to a ringing bell before dinner, and soon the rats would be showing elevated dopamine levels at the sound of the bell only--with no reward at all. Anticipation of reward was all it took. Or you could give one of the male rats a good close look at a suitable female through a mesh panel, and the male rat’s dopamine levels would surge, presumably in anticipation of possible carnal pleasures, and dopamine levels would spike even higher, of course, once the divider was removed.

Serotonin/dopamine dysfunctions cause physical discomfort, anxiety, and panic--what a renowned neuropharmacologist has termed “spiraling distress”—which continues to occur even in the complete absence of the addictive drug. Take the drug away, and the brain begins its complex and minutely ordered repertoire of compensatory effects--unpleasant sensations as read out by the addict.

Finding a way to override serotonin- and dopamine-mediated mid-brain commands is one of the keys to recovery from addiction. One of the aims of a biological understanding of addiction is to tease out the mechanisms by which
the reinforcing effects of addictive drugs become transformed into long-term adaptive changes in certain areas of the brain. “Why are we so surprised that when you take a poison a thousand times, it makes some changes in your head?” wondered James Halikas, who was co-director of the chemical dependency treatment program at the University of Minnesota during the crack heyday of the late 1980s and early 1990s. “It makes sense that poisons change things.”