

MANY NEUROLOGICAL DRUGS EXERT THEIR EFFECTS AT SYNAPSES

Because synapses act as control valves in the nervous system, and because their proper function depends on a very delicate balance between transmitter substance, deactivating enzyme, and membrane sensitivity, it is not surprising that synaptic malfunctions have been implicated in several mental disorders – among them schizophrenia – or that many neurological drugs exert their effects directly or indirectly at synapses.

Neurological drugs can alter synaptic function in a variety of ways. They may turn off certain synapses by:

- interfering with synthesis of the appropriate transmitter substance in the cell body of the neuron.
- interfering with the transport of the transmitter down the axon, from the cell body where it is synthesized to the synaptic terminal where it is packaged into synaptic vesicles.
- preventing release of the transmitter from the vesicles.
- blocking the receptor sites on the postsynaptic membranes, so that the transmitter has no effect even if released.

Other drugs can induce excessive and uncontrolled firing of postsynaptic cells by:

- stimulating massive release of transmitter substance from the vesicles.
- mimicking the effect of the transmitter.
- Inhibiting destruction of the transmitter once it has done its job. Cocaine, for instance, binds to and inhibits the protein responsible for removing the transmitter dopamine from dopamine synapses. Dopamine therefore remains active, producing overstimulation of postsynaptic neurons.

JUST SAY KNOW! NEUROMODULATORS AND PSYCHOACTIVE DRUGS

When an action potential spreads down an axon and reaches the presynaptic terminal, neurotransmitters (NT) and neuromodulators (NM) are released into the synaptic cleft. Depending on the receptor type at the other end of the cleft, the postsynaptic terminal, the actions of the NT or NM can vary. So, although it is important to realize that there is no single mechanism of action for each of the NTs or NMs (because there are many different kinds of receptors that can bind any single type of NT or NM), we *can* make some generalizations. Some of the main NTs that are found at nerve synapses are glutamate, GABA, glycine, and acetylcholine (ACh). These account for the majority of the nerve impulses that are sent throughout the body, and are found almost everywhere in the body. They bind to ion channel receptors, open channels, and let ions through that either depolarize or hyperpolarize the next cell. Usually glutamate and acetylcholine bind to excitatory (NA+) channels while GABA and glycine bind to inhibitory (Cl-) channels.

Compared to NTs, neuromodulators work a lot slower (seconds to hours), and are more involved in “setting the state” of the system. (They both work a lot faster than steroid hormones, though.) NMs are localized in the body, only being found at certain places where they are actively involved, and have longer lasting subtle effects. Like NTs, they are also released from nerve terminals and bind to receptors, but they usually activate 2nd messenger systems rather than sending ions in the next cell. You may recognize some of them: dopamine, serotonin, norepinephrine, and the peptides (enkephalins, endorphins, and Substance P).

Two of the most interesting NMs are dopamine and serotonin. Dopamine plays important roles in consciousness and mood states. It is associated with positive good things, and possibly with goal-oriented behavior. In experiments, animals that were able to stimulate these neurons by pressing a lever did so almost obsessively. Dopamine’s effects are seen in many common diseases, such as loss of motor functions, Parkinson’s disease (uncontrolled muscle tremors due to death of dopamine-releasing cells), and schizophrenia (too much dopamine released). Blocking dopamine receptors for schizophrenic patients removes hallucinations and revives normal thinking.

Serotonin is associated with depressive behavior, attention, sleep and dreaming regulation, and the perception of pain. Prozac, a commonly prescribed antidepressant, works by enhancing serotonin levels. Serotonin, like dopamine, is removed from the synaptic cleft eventually by a transporter pump, that uses a co-transport mechanism with Na+ to go back into the presynaptic terminal.

Many of today’s “**street drugs**” function as competitive inhibitors of the body’s own NMs. **Cocaine** binds to allosteric sites on the receptors of dopamine transporter pumps, located on the presynaptic membrane. They block the reuptake of dopamine, so that it stays around about 100 times longer than normal. **Amphetamines** (such as speed), also block the dopamine transporter pump, and in addition, make the pump run backwards. This brings even more dopamine into the synaptic cleft, making them more powerful drugs.

Ecstasy is another street drug often used at Rave parties and is associated with pleasure, empathy towards others, and a general feeling of happiness. People who take

ecstasy often feel the urge to hug and be in physical contact with other people. Ecstasy works by affecting both dopamine, and mostly serotonin transporters. It acts like amphetamines by blocking the uptake pumps and causing them to run backwards. Unfortunately for anyone with prolonged ecstasy use, it is toxic to nerve terminals and noticeably kills brain cells. This may be due to ecstasy's backward pumping action. Prozac, which also blocks serotonin reuptake without reverse pumping action, does not kill brain cells. Based on this, one might expect amphetamines to also kill brain cells. Based on this, one might expect amphetamines to also kill brain cells, since they both block dopamine reuptake along with turning the pump backwards. And in fact, we can see actual degeneration of some matter in the nerve terminals of basal ganglia.

Marijuana doesn't block receptors like the other drugs discussed so far. Actually, it binds to and activates receptors in our brain that seem to be meant for a set of biologically produced compounds called arachidonic acids, a set of fatty acids with NH_2 groups. Marijuana has a stronger effect than these, however. It reduces cAMP levels in the frontal cortex (involved in space/time) and motor areas, which can be seen from its bodily effects: inhibiting learning from occurring and impaired motor coordination during use.

The peptide NMs also bind to receptors and activate a second messenger cascade. There are no transporter pumps to uptake them, so they are long lasting (up to hours) and eventually degraded by peptidases. Substance P enhances the perception of pain. Conversely, enkephalins and endorphins, a set of related compounds, suppress pain signals. Endorphins are what some athletes associate with a "runner's high." **Heroin** is an agonist to endorphins – it mimics them and binds to the same receptors, producing the same effects yet much stronger. One question to think about is why the body, over our long period of evolutionary history, never began to synthesize these drugs with the same effects as our natural chemicals (yet often stronger)?