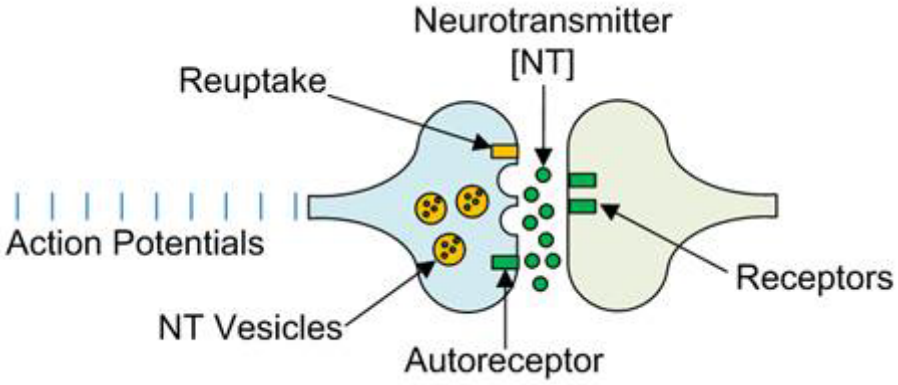
TREMOREX v DRUGS

Drugs seek to mitigate movement disorders by modulating synapses.

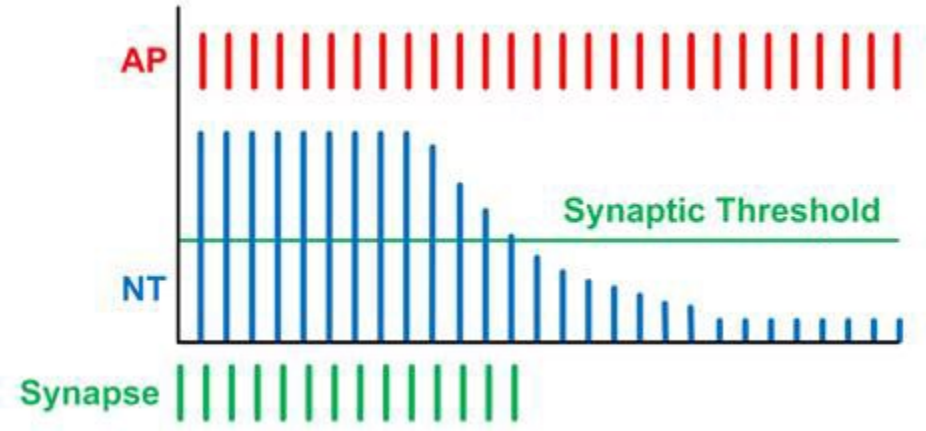
Normal Synapses



The figure illustrates a synapse wherein an adequate amount of Neurotransmitter [NT] is released per Action Potential [AP] for an Action Potential Rate [APR] within the normal range. NT vesicles are held in the reserve pool for occasional high APR episodes

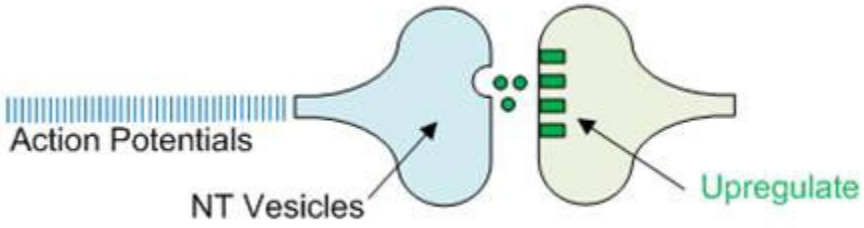
A failure to communicate
When a presynaptic neuron does not release enough NT per AP, the synapse is likely to fail and that is a failure to communicate.

Synaptic Fatigue
An AP causes a release of NT into the synaptic cleft. NT is packaged in vesicles and stored in ready and reserve pools. The amount stored is based on normal demand with enough reserve to handle occasional high APRs. If the APR is very high or high for a sustained period, synaptic vesicle pools will be depleted, and synapse will fail.



A loss of synapses occurs when synaptic fatigue is experienced. The sustained high APR depletes the NT vesical pools faster than the pools can be refreshed.

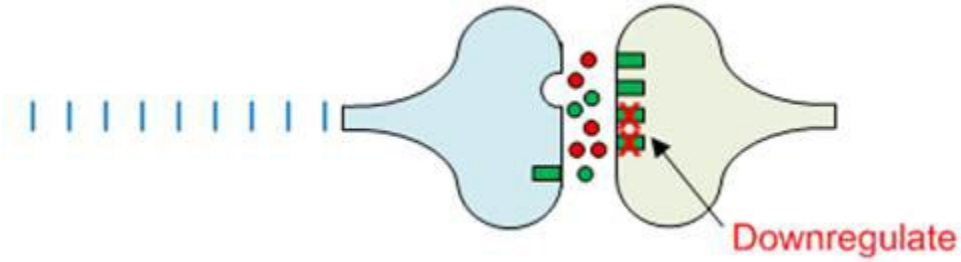
Synapse with synaptic fatigue



The figure illustrates the effect of inadequate NT vesicles when APR is beyond normal. The vesicle pool is depleted, there is inadequate NT in the synaptic cleft, and the number of active receptors has increased to compensate for the deficit NT. This is not unlike turning up the volume control to compensate for a weak radio signal.

DRUG therapy mechanisms
Drugs seek to correct the deficit by modulating the synaptic process. Four preferred methods are 1) agonist drugs, 2) antagonist drugs, 3) Reuptake Transporter Inhibitors and 4) L-Dopa.

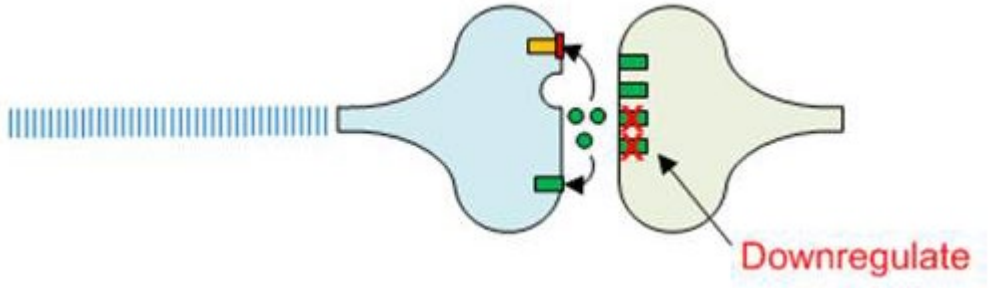
Agonist drugs
Red circles are drugs that mimic the endogenous [naturally produced] NT, green circles, and flood the synaptic cleft to provide higher probability the postsynaptic neuron will fire.



However, that causes homeostasis downregulation in the postsynaptic neuron, reduction in the number of active receptors, as a greater than “normal” amount of NT is in the synaptic cleft. In addition, the closed loop circuit that controls the amount of endogenous NT released is disrupted because the density of the NT returned via Autoreceptors is overstated. Over time, homeostasis downregulation causes the neuron to decrease the amount of NT vesicles being synthesized, stored, and the amount of NT released per AP.

Antagonist drugs [not shown] block receptors thereby decreasing the probability endogenous NT will cause the postsynaptic neuron to fire. Continuous drug therapy over a protracted period causes an increase in the number of receptors, as a less than a “normal” amount of NT binds with the receptors and an increase in the amount of NT released as the Autoreceptors are also blocked.

Reuptake Transporter Inhibitors –impede the reuptake of NT in the synaptic cleft providing a higher probability the postsynaptic neuron will fire.



Aside from disrupting the normal function of evacuation and reuse of NT by the presynaptic neuron, the postsynaptic neuron experiences a more than "normal" amount of NT and responds by homeostasis downregulating the number of its active receptors. And because the Autoreceptor is overstimulated, less NT is released per AP.

L-Dopa, the gold standard treatment for Parkinson's Disease
It is widely accepted that Parkinson's Disease is attributable to insufficient levels of dopamine. It is largely unknown why the number of and/or the production capacity of dopaminergic neurons is diminished; whether they have lost their capability or the demand upon them has decreased. Research has evidenced that "dopaminergic neurons that do not release dopamine exhibit normal activity". This suggests that the neurons are able but inadequately stimulated. Nevertheless, treatment to increase dopamine release centers on providing more raw material, L-Dopa, from which dopamine is synthesized. Increase raw material and more product will be produced.

In all cases, drugs seek to "help" synapse
But when exogenous interventions are used to "help" endogenous processes, homeostasis is inadvertently effectuated to regulate in the wrong direction. Regulation follows activity, decrease activity and endogenous processes weaken. This is analogous muscle atrophy due to inactivity.

Decrease demand on a neuron and its ability to perform decreases
Drug therapy may mitigate symptoms, but it causes change to neurons that then require higher drug dosage that change neurons that >>>. This vicious cycle can lead to drug dependency and acceleration of neuronal atrophy.

Furthermore, drugs are systemic. They enter the bloodstream and go everywhere. Whereas they may be beneficial in one area, they may be detrimental in another. That's one of the causes of those dreadful side effects.

Drugs have an efficacy curve that has nothing to do with endogenous neuronal activity. Their presence is not in response to or in sync with neuronal stimulation. They do not react to or enhance the presynaptic neuron sensitivity to stimuli, the production of AP and the release of NT into the synaptic cleft. They do not enter and evacuate the synaptic cleft in sync with endogenous events. Drug mechanisms interfere with endogenous mechanisms and serve to artificially change the threshold of postsynaptic neuron receptors.

TREMOREX

Whereas drug therapy seeks to **modulate** synapses, TREMOREX seeks to **restore** synapses and all the other processes involved in the execution of a muscle memory.

Drugs modulate synapses, TREMOREX restores movement disorders

Note, whereas the mechanisms are quite different, it was unexpectedly observed that TREMOREX was highly effective while subjects were on drug therapy.