Master /Bachelor Thesis Project
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Nano-Pharmacology

Drug selectivity and binding modes in monoamine transporters

Monoamine transporters are a class of membrane proteins, which regulate neurotransmission by reuptaking the released monoamines back into the presynaptic neurons. They are drug targets in the treatment of various diseases, including depression, attention deficit hyperactive disorder (ADHD), drug abuse, etc. Understanding the binding modes of drugs that affect the monoamine transporters is essential to explain their mechanism of action and to develop new and improved therapeutic compounds. Selective drugs are desired in the treatment of particular diseases. For example, it is beneficial to treat depression by inhibiting serotonin transporter (SERT), but not dopamine transporter (DAT). Conversely, only inhibitors of DAT and norepinephrine transporter (NET) ameliorate the symptoms of ADHD.

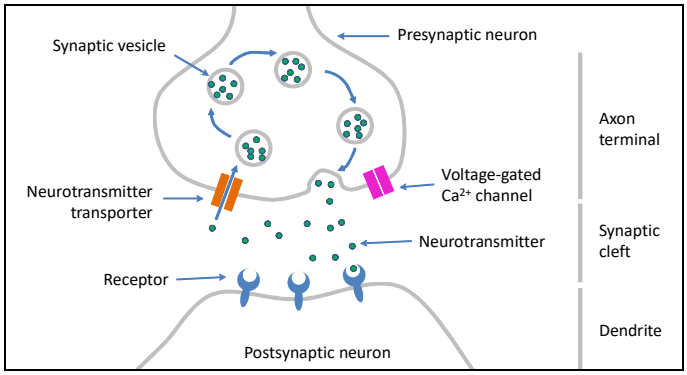

Figure 1 - *Neurotransmitter transporter can reuptake the neurotransmitters from the synaptic cleft into the presynaptic neuron, thus terminating the neural signal transmission.*

Our research project aims to examine the kinetics and binding energy landscapes of ligands and substrates with neurotransmitter transporters on the single molecule level. This will be achieved by measuring interaction forces with atomic force microscopy (AFM) – based single molecule force spectroscopy (SMFS).

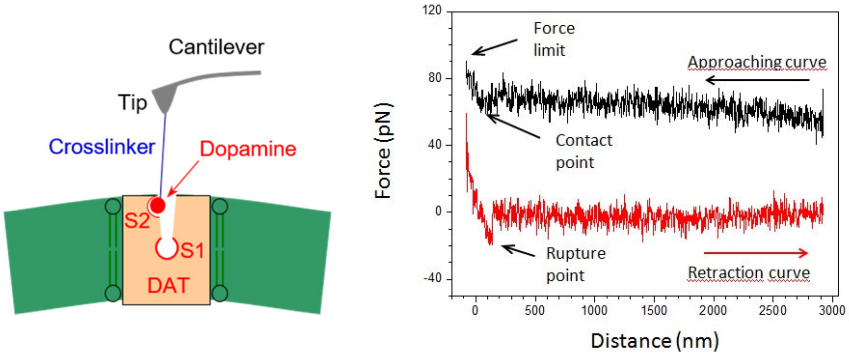

Figure 2 - AFM C*antilever tip is functionalized with dopamine via PEG crosslinker (left panel). Force spectroscopy measurements are performed on CHOK1 cell expressing DAT. Example force curve in right panel. Rupture point of the red trace reflects dissociation of drug from transporter.*

Tasks performed by the student:

- Tip-chemistry: Functionalization of AFM cantilever tips with drug molecules, such as desipramine, methylphenidate, etc.
- Force spectroscopy: Using Atomic Force Microscopy (AFM) to measure interaction forces between drug molecules and DAT or SERT in the cell membrane.
- Data evaluation and extraction of interaction force, kinetic rate constants, k_{on}, k_{off}, etc.

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