Lecture 8 – Synaptic Transmission III – Kandel

I. Role of Ca^{++} in Release of Transmitter
- A. Experiments of Katz
  - 1. used external TTX and internal TEA^{+} to block, respectively, voltage-dependent Na and K channels and show that those ions do not directly trigger release
  - 2. block of K channels can actually increase release by preventing sag in depolarization
  - 3. increased $[Ca^{++}]_o$ causes increased release; removal of Ca^{++} from extracellular medium blocks release
  - 4. external Ca^{++} required at time of presynaptic depolarization; not effective if only present shortly after depolarization
  - 5. miniature end plate potentials (mepps) occur in absence of presynaptic depolarization
  - 6. stimulation of motor neuron in very low $[Ca^{++}]_o$ results in some failures and some epps whose amplitudes are multiples of mepp size
  - 7. conclusions
    - a. transmitter released in quantal packets (synaptic vesicles)
    - b. each quantum contains a standard amount of transmitter (~ 5000 molecules of acetylcholine per quantum at the NMJ)
    - c. influx of Ca^{++} through voltage-dependent Ca channels (which are concentrated at presynaptic terminal) increases the probability of vesicle release, rather than the size of individual quanta

II. Steps in Release
- A. Exocytosis
  - 1. vesicle brought into close contact with presynaptic plasma membrane by binding of vesicle SNARE (VAMP/synaptobrevin) to plasma membrane SNAREs (syntaxin and SNAP-25)
  - 2. release occurs by fusion of vesicle and plasma membranes, opening inside of vesicle to synaptic cleft so that transmitter can diffuse out
  - 3. NSF catalyzes dissociation of the SNAREs to allow reuse
- B. Mobilization
  - 1. large pool of synaptic vesicles stored in reserve away from plasma membrane by linkage to cytoskeleton via synapsins
  - 2. influx of Ca^{++} can release these vesicles to allow them to move up to release sites to allow synaptic release of transmitter to continue
- C. Docking
  - 1. vesicles are brought into place close to the release site
  - 2. influx of Ca^{++} stimulates exocytosis of docked vesicles

III. Plasticity of Synaptic Release
- A. Intrinsic regulator
  - 1. posttetanic potentiation caused by saturation of Ca^{++}-buffering systems in terminal resulting in high baseline $[Ca^{++}]_i$ to which subsequently triggered Ca^{++} influx adds
- B. Extrinsic regulators
  - 1. presynaptic inhibition
    - a. caused by release of inhibitory transmitter onto presynaptic terminal
    - b. distinctive features compared to postsynaptic inhibition
      - i. synapse-specific
      - ii. long-lasting
  - 2. presynaptic facilitation
    - a. can work directly on exocytotic machinery or by broadening presynaptic action potential

IV. Unsolved Questions

A. What are the complete molecular details of the regulation of transmitter release?

B. How do long-term changes in synaptic plasticity (≥days) occur?

C. How do synaptic changes map onto behavioral phenomena?