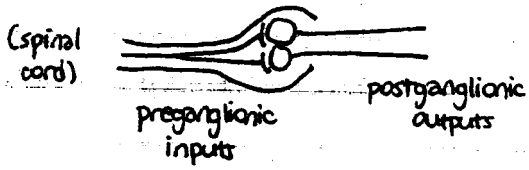
3/10/04

review session: Sun. afternoon 3pm

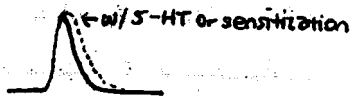


(1 synaptic layer)

- in Aplysia, Kandel etc. looked for changes in presynaptic cell (b/c sensitization → higher lower m ...?)
  - can't record from presynaptic terminal, so looked in cell body (lower P_o)

sensory neuron

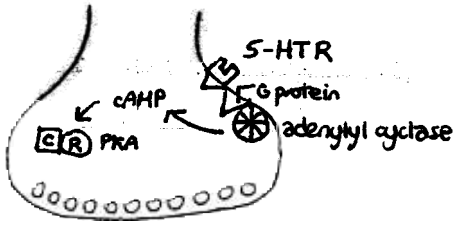
↑ tickle gill
- tickling cell gives AP
- after sensitization or applying 5-HT, AP can turn broader



spike broadening

(even broader if block Ca^{2+} channels)

- spike broadening consequence of cAMP ↑?



- PKA usually has regulatory & catalytic subunits bound (turned off): tetramer
  cAMP binds 2 sites on R, releases C, can go phosphorylate stuff

- Kandel et al injected:
  1. catalytic subunit (got spike broadening)
  2. superregulatory protein ("Walsh inhibitor"): regulatory subunit w/ no cAMP-binding sites; constitutively turns off PKA (this protein is PKI)
     - injecting PKI blocks spike broadening & synaptic effect (potentiation)

- PKA can phosphorylate channel: activate depolarizing or inactivate hyperpolarizing channel
  - found that K^+ channel inactivated

- patch-clamped sensory neuron, pulled off patch (w/ channels): cytoplasmic face outside
  - applied voltage clamp, found noise (in 2, 3, 4 quanta): 4 channels on membrane patch, open most of time
  - apply catalytic PKA subunit, get average of 1-2 channels, get recovery (quicker if treat w/ phosphatase)
  - K^+ channel tries to keep membrane repolarized (K^+ S channel); PKA phosphorylates + closes, lose some repolarizing K^+ current during AP, get spike broadening
  - broadening AP keeps cell depolarized longer, more Ca^{2+} influx, more transmitter release

if touch one part of gill, give tail shock, touch another part w/ no tail shock, both parts sensitized
- pairing - specific component on top of general sensitization, however

- can take identified abdominal ganglion neurons (sensory + motor), just cell bodies, need serotonergic neuron too to apply low [5-HT], make other two types grow, get synapses
  - applying 5-HT gives synaptic facilitation in dish as well as in animal
  - will usually last 10-20 minutes
    - if apply 5 pulses ~ 1 minute apart, get synaptic facilitation that lasts 24 hours: long-term memory in dish
      - block long-term memory w/ inhibitors of transcription + translation (doesn't block short-term form)
        - long-term synaptic facilitation requires protein synthesis
          CREB transcription factor regulates gene expression downstream of cAMP

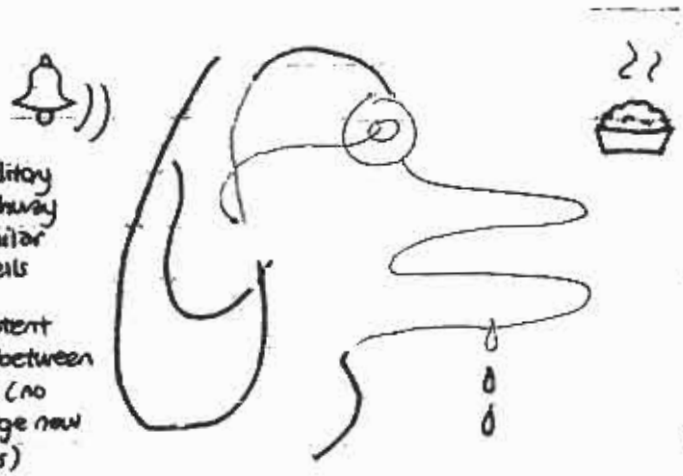
- inject Anti-CREB (Aplysia) into nucleus of sensory neuron, blocks synaptic facilitation 4 mediated by this transcription factor

(this is also true in mice + flies: blocking CREB gets rid of long-term memory)

sensitization - general increase in responsiveness after strong or noxious stimulus
(eg chip screaming or poking gill w/ electricity)

classical conditioning:

- stimulus like bell (normally no response) (CS)
- pair bell w/ food : training
  - ↳ (normally gives salivation) US (or reinforcement): food is positive reinforcement
- testing afterwards, bell alone gives salivation
  - ↳ trained responsive specific to paired one: must be sound of this bell



bell sound goes to auditory cortex, pathway goes to similar premotor cells

- must be latent connection between ear + drool (no time to forge new connections)

food goes to visual cortex? pathway goes to premotor cells, gives you drool reflex

synapse A always excitatory: boring

- constitutively excitatory

synapse B is Hebbian synapse

- initially ineffective (no drool)
- strengthened by paired training, eventually sound alone gives drool

this is a dog

dog becomes simultaneity detector

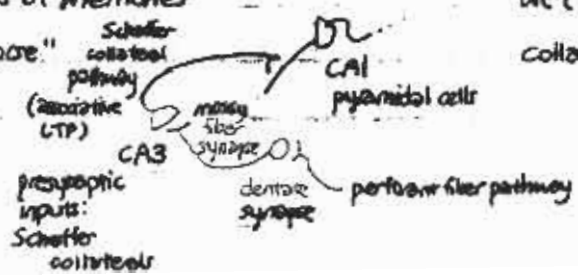
want synapse to become simultaneity detector

- strengthened if presynaptic + postsynaptic cells fire together

- "cells that fire together wire together"
- Hebb found simplest synapse that show this
  - initially no effect at synapse
    - more + more firing together = more strengthening of synapse

HM - bilateral medial temporal lobe lesions, including hippocampus

- need hippocampus to store a class of memories
  - hippocampus curled up, "sea horse"
  - circuit is simple (trisynaptic)



we care about Schaffer collateral pathway

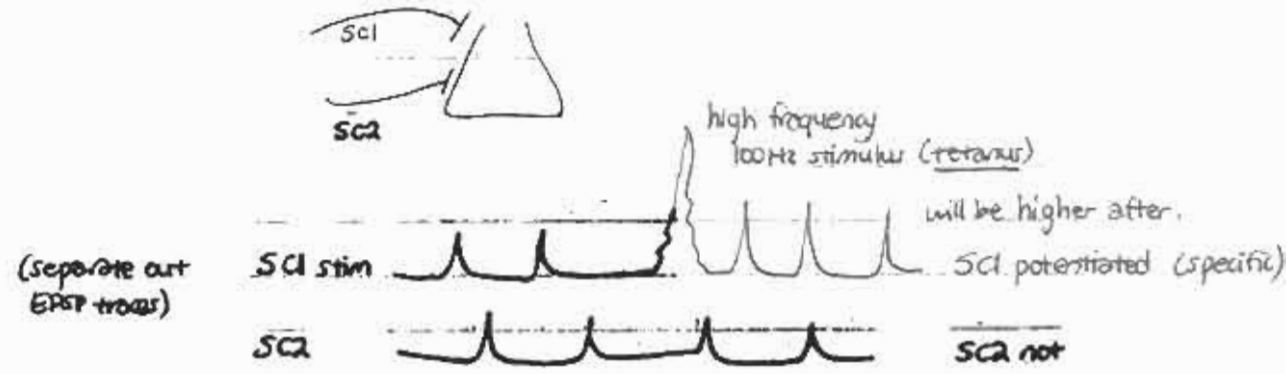
- mouse hippocampus has same neuroanatomy as human

- hippocampal defects: can't recognize new faces, remember events
  - in mouse, test w/ Morris water maze (pool, circular, full of opaque liquid, w/ hidden platform; mouse will swim until finds hidden platform)
    - can train mouse to know where platform is, w/ external room cues to navigate
      - removal of hippocampus removes this ability

stimulate Schaffer collaterals, record intracellularly in postsynaptic CA1 cell:
- get EPSP at certain frequency
- give stimulus, eg 100 Hz; afterwards, get bigger EPSP, then goes back
  ↳ potentiation

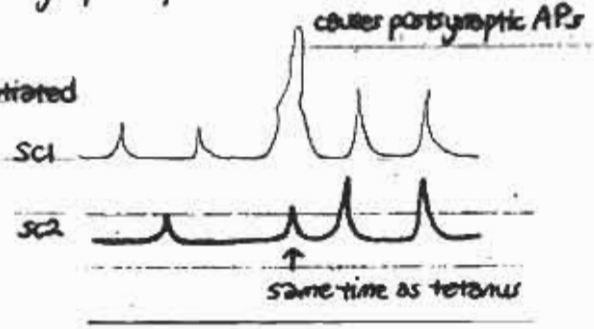
LTP in Schaffer collateral pathway

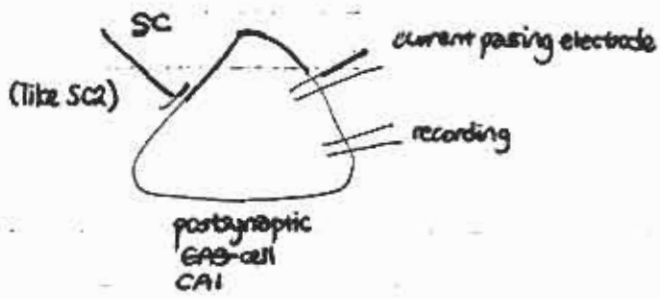
- 2 inputs 2 regions of Schaffer collateral that are separate, stimulate different fibers



- long-term potentiation is synapse-specific

- if fire SC2 during SC1 tetanus, both are potentiated
  "cells that fire together wire together"





- presynaptic firing during postsynaptic depolarization while will give LTP (potentiation)
- no potentiation if current keeps V_m at resting during presynaptic tetanus
- cells as simultaneity detector: presynaptic firing + postsynaptic depolarization

- neurotransmitter used in these cells is glutamate
  - 2 interesting types of GluRs on postsynaptic membrane:
    1. AMPA R: ~~antagonist~~ antagonist (CNQX), agonist = AMPA
    2. NMDA R: antagonist (APV or AP5), agonist = NMDA

- applying CNQX blocks almost all synaptic transmission
  - AMPA R conducts 95% of inward excitatory current in EPSP
- applying APV blocks only 5% of EPSP, but blocks LTP almost completely

- AMPA Rs conduct Na^+ (almost purely)
  NMDA Rs conduct Na^+ + Ca^{2+}
  - Synaptic plasticity depends on NMDA Rs
    ↳ ligand-gated channel opened by glutamate (↓ antagonist agonist NMDA)
    - unless depolarized, Mg^{2+} will block channel, no Ca^{2+} influx

this channel itself is Hebbian simultaneity detector: need presynaptic activity (→ glu) and postsynaptic activity (depolarization of V_m) to open, let in Ca^{2+}
(w/o Mg^{2+}, don't need depolarization for Ca^{2+} conductance)