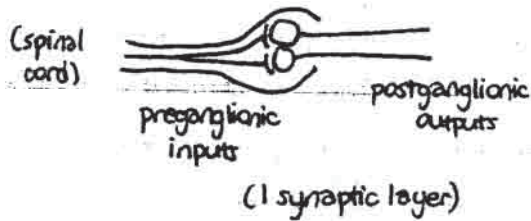


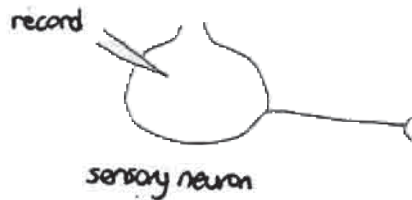
Lecture notes courtesy of Wyan-Ching Mimi Lee. Used with permission.

3/10/04

review session: Sun. afternoon 3pm

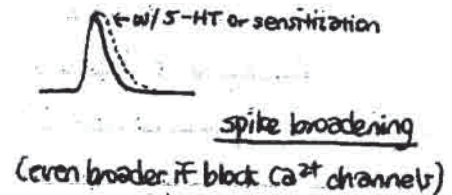
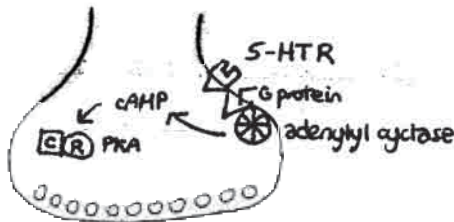


- in Aplysia, Kandel etc. looked for changes in presynaptic cell (b/c sensitization → higher m...?)
- can't record from presynaptic terminal, so looked in cell body (lower  $P_0$ )



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

- 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

Anti-CREB (Aplysia) into nucleus of sensory neuron, blocks synaptic facilitation

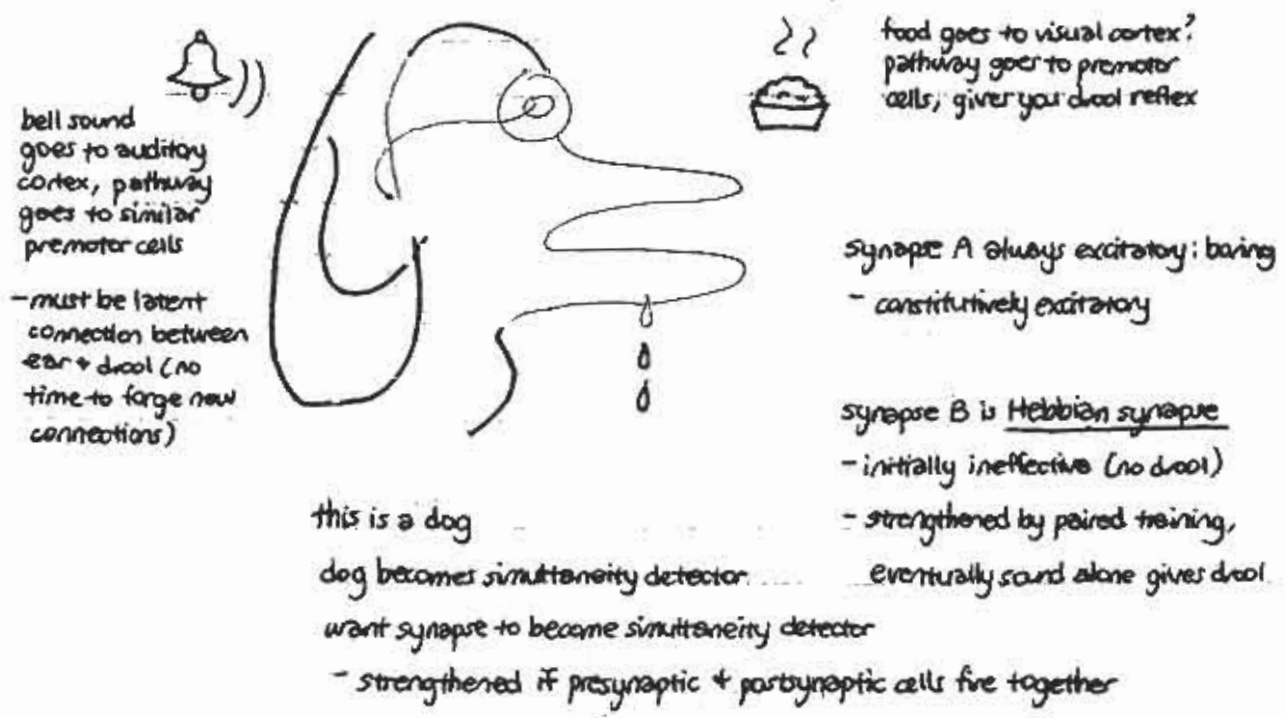
↳ mediated by this transcription factor

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

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

classical conditioning:

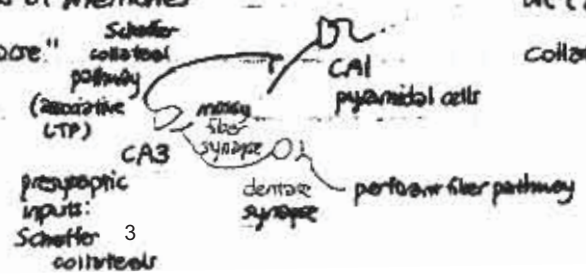
- stimulus like bell (normally no response) (CS)
- pair bell w/ food : training
  - ↳ (normally gives salivation) US (or reinforcement): food is positive reinforcement
- testing afterwards, bell alone gives salivation
  - ↳ trained responsive specific to paired cue: must be sound of this bell



- "cells that fire together wire together"
- Hebb found simplest synapse that shows 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

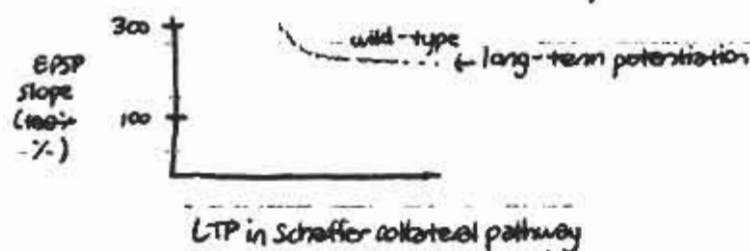
- removal of hippocampus removes this ability

stimulate Schaffer collateral, record intracellularly in postsynaptic CA1 cell:

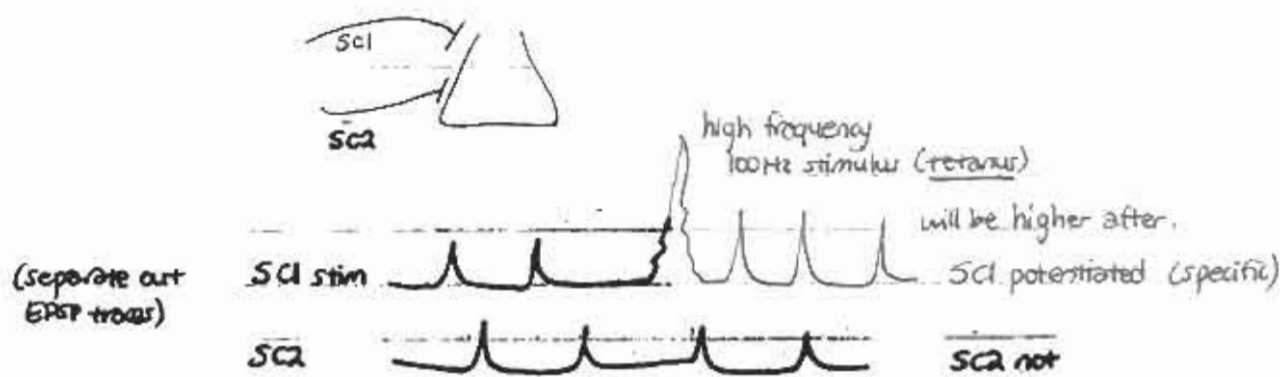
- get EPSP at certain frequency

- give stimulus, eg 100 Hz; afterwards, get bigger EPSP, then goes back

↳ potentiation



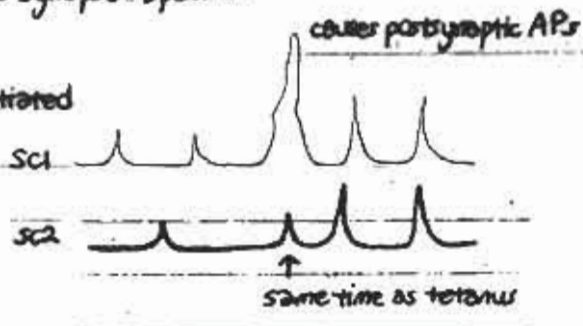
= 2 inputs 2 regions of Schaffer collateral that are separate, stimulate different fibers

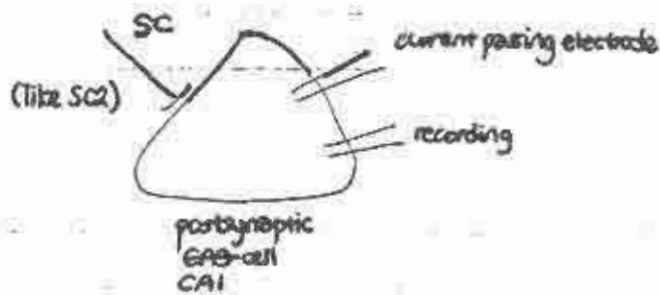


- long-term potentiation is synapse-specific

- if fire SC2 during SC1 tetanus, both are potentiated

"cells that fire together wire together"





- presynaptic firing during postsynaptic depolarization 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,  $Hg^{2+}$  will block channel, no  $Ca^{2+}$  influx

this channel itself is Hebbian simultaneity detector: need presynaptic activity ( $\rightarrow$  glu)

and postsynaptic activity (depolarization of  $V_m$ ) to open, let in  $Ca^{2+}$

(w/o  $Hg^{2+}$ , don't need depolarization for  $Ca^{2+}$  conductance)

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