3/8/04

quantum = postsynaptic response to one vesicle released

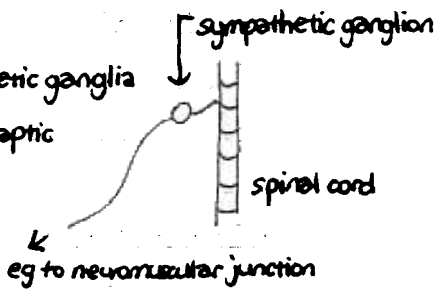
Orbelli effect: presynaptic: sympathetic axons release norepinephrine (makes quantal content go up from motor axons)

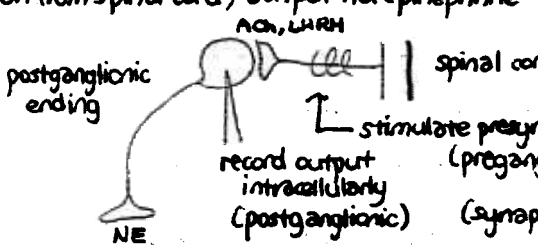
postsynaptic: adrenal gland releases epinephrine, plugs up muscle cell leakage channels (increases R so ΔV greater)

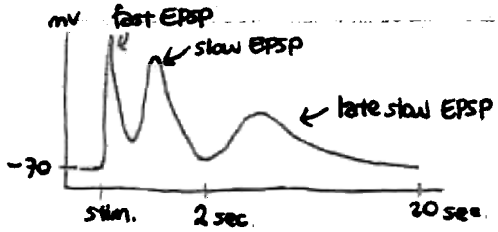
- pharmacological dissection
  - α - adrenergic receptors (presynaptic): ~~agonist = isoproterenol (used for anaphylactic shock)~~
    ~~antagonist = β - propanolol (used for heart patients, stage fright)~~
    agonist = norepinephrine
    antagonist = clonidine
  - β - adrenergic receptors (postsynaptic): agonist = isoproterenol (used for anaphylactic shock)
    antagonist = β - propanolol (used for heart patients, stage fright)
- principle here is <u>synaptic modulation</u> (volume control : modulatory neurotransmitters, eg epinephrine, norepinephrine

- blurring of function between neurotransmitters + hormones (eg norepinephrine released in vicinity of neuromuscular junction, acts semi-locally, diffuses more) (epinephrine acts not at all locally)

sympathetic ganglion:
- pioneering work done in bullfrog
  - in our sympathetic nervous system, have adrenal gland + sympathetic ganglia
    - in spinal cord is lump of nerve cells, some interneurons : presynaptic axon from spinal cord, output norepinephrine







1 stimulation, 3 potentials recorded from 1 cell

- ganglia have lots of ACh : spritzing ACh gives 2 out of 3 (fast + slow EPSPs)

1 kind of neurotransmitter effects 2 different type of receptors (only one blocked by curare: blocks fast but not slow or late slow)

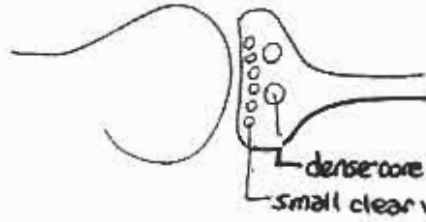
atropine - another cholinergic antagonist

- belladonna used to dilate pupils; atropine is active ingredient (-taking too much is lethal)
  - ↳ (Atropos is Fate w/ scissors, cuts off human life)
- blocker for 2nd class of cholinergic receptors ↓ ionotropic (ligand-gated channel)
  - neuromuscular junction receptor: nicotinic AChR (agonist = nicotine) (antagonist = curare)
  - 2nd class of receptors (dominant on heart cells): muscarinic AChR (ie metabotropic, 2nd messenger coupled)
    - ↳ like Loewe's vagus nerve heart experiments
    - (agonist = muscarine) ← from Muscaria mushroom, insecticide
    - (antagonist = atropine)

- applying curare gets rid of fast EPSP
  applying atropine gets rid of slow EPSP (so slow EPSP from atropine working on mAChRs)

- mAChR 2nd messenger system: patch clamping shows that stimulation w/ ACh <u>closes</u> K+-type channel (K^+ channel): closing K^+ channel is excitatory/ depolarizing, gives you slow EPSP

late slow EPSP :

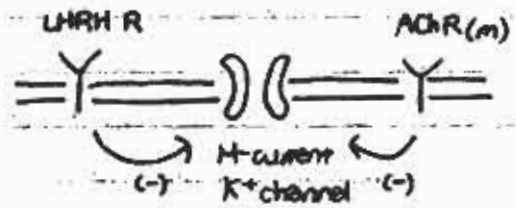


contain lots of things, including peptide neurotransmitters
- got Abs to these peptides, eg LHRH
  - ↳ from rat estrus cycle, makes luteinizing hormone in pituitary

- System of tiny hormones in rat pituitary tells it to release other hormones (or something)

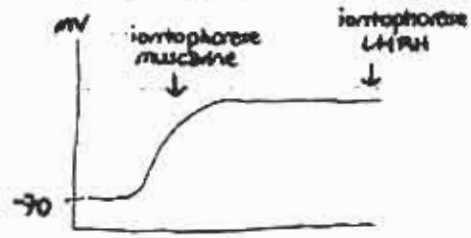
spritzing LHRH on sympathetic ganglia give you late slow EPSP

- can have 2 synaptic messenges released from same sympathetic ending



mAChR + LHRH R metabotropic

- occlusion experiments:
  - record from postganglionic cell



no additional response: muscarine occludes effect of LHRH
- downstream pathways converge, so saturating w/ one input (all K^+ channels closed) means other input will have no effect
- not order-dependent

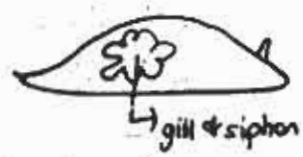
- used to test for convergent downstream effector (eg same or different 2nd messenger systems, but converge eventually)

- in sympathetic ganglion, B & C cells
  - ↳ big
  - ↳ not big

spritzing LHRH on C give no effect
spritzing on B gives late slow EPSP

- LHRH effect only seen on B cells (only B cells have late slow EPSP)
  - paradox is: immunoreactivity (LHRH vesicles) only seen on presynaptic endings to C cells
  - Ach released conventionally across synaptic cleft for both B & C cells
    - LHRH diffuses from synaptic cleft of C cells to that of B cells, late slow EPSP (blurring of transmitters / hormones, localization of action) ↳ (partly b/c of diffusion)
  - this is interesting b/c shows you electron microscopy not infallible: must confirm w/ electrophysiology

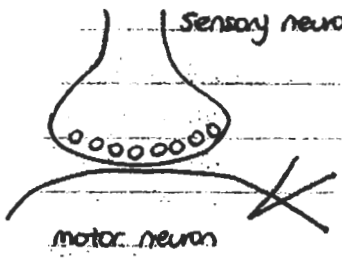
Aplysia californica californica: "sea hare" (but is basically sea slug): lives in tide pool, eats kelp (will eat kimuipes)



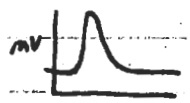
squirt terrible-smelling purple ink

- have 7 ganglia, 20,000 cells (very large)
  - reproducible arrangements of cells, eg all abdominal ganglia same

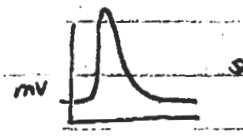
- Eric Kandel did circuit-tracing in Aplysia for gill-withdrawal reflex (poking in gill causes gill to withdraw)
  - can get contraction that can be measured in muscle: eventually, will get habituation (waning in strength of reflexive response)
  - give strong tail shock: this sensitizes
- sensory neurons make monosynaptic connections on motor neurons that contract gill
  - all cells in abdominal ganglia: tail shock gives you greater reaction, after many days will get permanently larger reaction (sensitization is opposite of habituation)



record intracellularly for EPSP



this reflex comes w/ memory, can be related to synaptic events (can only be done in this system)



~~sensiz~~ sensitization (more efficient synaptic transmission: synaptic facilitation)

habituation

- what causes these changes? (sensitizing us: release epinephrine & norepinephrine)
  - biogenic amines: 5-HT, epinephrine, dopamine, ACh, norepinephrine, etc in us
    5-HT, dopamine, octopamine in animals (epinephrine w/o HO)
  - sensitized bunch of animals, found out 5-HT ↑ (measured neurotransmitter levels
    dopamine ↑ in abdominal ganglia)
    octopamine ↑
    - spritzed these, found that only 5-HT gave change (synaptic facilitation)
      - long responses require 2nd messenger systems coupled to metabotropic receptor (at this time, only cAMP 2nd messenger system understood: spritzing 5-HT → cAMP↑)
- synaptic facilitation presynaptic or postsynaptic ? lower $[Ca^{2+}]$, do quantal analysis, found ~~increased~~ decreased probability of failure (so presynaptic): cAMP activates kinase, blocking kinase blocks effect