It's a rather interesting phenomenon. Every time I press this lever, that post-graduate student breathes a sigh of relief.
neurotransmitters: mediating information exchange between neurons through generation of synaptic potentials

three basic types of neurotransmitter:
1. ionotropic excitatory (glutamate, ACh) – cause EPSPs
2. ionotropic inhibitory (GABA, glycine) – cause IPSPs
3. metabotropic / neuromodulatory (norepinephrine or ‘NE’, serotonin or ‘5-HT’, dopamine or ‘DA’, histamine or ‘HA’, acetylcholine or ‘Ach’)

EPSP and IPSP

- EPSP: excitatory post-synaptic potential (EPSP)
- IPSP: inhibitory post-synaptic potential (IPSP)
characteristics of brain neuromodulatory systems:

1. small groups of neurons (10’s of thousands) sharing the same neurotransmitter (i.e., neuromodulator)

2. projections, via unmyelinated fibers, to widespread regions of the brainstem and forebrain

neuromod. system | projection pattern | histology

noradrenergic (NE): main nucleus is the locus coeruleus in the pons

dopaminergic (DA): ventral tegmental area and substantia nigra area (both in midbrain) – note more localized projections

tyrosine (OH) \[\text{Fe}^2+, \text{O}_2, \text{BH}_4^- \rightarrow \text{Tyrosine hydroxylase} \rightarrow \text{L-DOPA} \rightarrow \text{dopamine} \rightarrow \text{norepinephrine} \]
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- **cholinergic (NE):** pontine and basal forebrain groups

- **serotonergic (5-HT):** several raphe nuclei distributed in brainstem

- **histaminergic (HA):** the ‘forgotten one’ – neurons localized to posterior hypothalamus
characteristics of brain neuromodulatory systems:

3. neurotransmitter binding to receptors generates, through phosphorylation, long-lasting (100+ ms) changes in properties of voltage-gated ion channels

2 examples of metabotropic pathways by which neuromodulators affect target neurons:

1) Cyclic-AMP pathway
2) Phospoinositide (IP3) pathway

Both activate protein kinases that phosphorylate ion channels thereby changing membrane potential and/or membrane potential responses to activation of ionotropic receptors
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*ion selectivity – e.g., Na+, Ca++, K+, Cl-

*gating – e.g., by voltage, ligand

*kinetics – e.g., open-time

*state – e.g., activated, inactivated, deinactivated, persistent, phosphorylated

*distribution – e.g., in dendrites, at axon hillock
characteristics of brain neuromodulatory systems:

4. firing activity of neuromodulatory neurons is strongly impacted by sleep/wake state (exception for dopamine)

cholinergic (NE): basal forebrain

noradrenergic (NE): locus coeruleus
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5. neuromodulatory neurons receive input from a number of different sources, but all receive input from prefrontal cortex

6. low firing rates (mean approx. 0-6 Hz)

7. influence the neuronal responses to ionotropic excitatory and inhibitory inputs as opposed to directly mediating excitatory or inhibitory responses (i.e., alter the ‘functional anatomy’ of the brain)
neuromodulation I: alteration of ion channel kinetics through changes in phosphorylation state

Desai and Walcott, 2006: ACh decrements the responses of Ca++-dependent K+ channels thereby enabling greater initial responses as well as persistent responses to current injection (note...current injection mimics excitatory ionotropic input)

**What**

1. ACh agonist application (i.e., activation of ACh receptors)
   - current injection

2. ACh agonist application (i.e., activation of ACh receptors)
   - increasing current injection steps
   - persistent firing rate response to short-term excitatory input

**Why**

3. Change in membrane potential in response to neuromodulatory inputs is sometimes minimal

4. Persistent firing response may, in turn, be modulated by number of excitatory inputs

5. ACh alters K+ outflow caused by Ca++ influx (as seen when excitatory ionotropic receptors are activated)
neuromodulation II: uneven distribution across dendrites, of ion channel responses to neuromodulators leads to alteration of neuronal responses to intrinsic, but not extrinsic inputs in pyriform cortex

Hasselmo et al., 1997: both norepinephrine and acetylcholine depress synaptic responses to excitatory inputs in layer Ib (intrinsic connections) much more so than to excitatory inputs to layer Ia (extrinsic connections) – that is, each change the degree to which pyriform cortex listens to the outside world (extrinsic inputs) versus the inner world (cortex→cortex or ‘intrinsic’ inputs)

layer Ia inputs to dendrites of layer II neurons arise from olfactory bulb

layer Ib inputs to dendrites of layer II neurons arise from other regions of cortex

in this case, both acetylcholine (mimicked by carbachol) and norepinephrine have the same action on Ib inputs

excitatory responses to layer Ia or Ib stimulation under different conditions
the long reach of neuromodulatory systems

drugs of abuse associated with neuromodulatory systems:

ACh: nicotine

5-HT: LSD, *ecstasy, ‘magic’ mushrooms

NE: yohimbine

DA: *heroin, *amphetamines (e.g., ‘ice’), *cocaine (also ‘crack’)

HA: ?

treatment drugs associated with neuromodulatory systems:

ACh: donezepil (Alzheimer’s)

5-HT: prozac (depression, obsessive-compulsive disorder, anxiety)

NE: desipramine (depression)

DA: thorazine (schizophrenia), L-DOPA (Parkinson’s disease), Ritalin (attention deficit disorder)

HA: antihistamines (insomnia)

neurological disorders associated with neuromodulatory systems:

ACh: Alzheimer’s

5-HT: depression

DA: schizophrenia, Parkinson’s disease
mediation of drug reward through the brain’s reinforcement learning mechanism

1. rats learn what to do to obtain VTA stimulation very quickly

2. mechanisms of drug action on the dopaminergic projection to nucleus accumbens (NAc):
   - cocaine – blocks clearance of dopamine from synapse onto NAc neurons (reuptake inhibition)
   - heroin – inhibits GABA neurons that inhibit dopamine (DA release increases through ‘disinhibition’)
   - nicotine – directly excites dopamine neurons
   - amphetamines – increase dopamine release through action at the axon terminal

3. Parkinson’s disease patients (who have <10% the normal amount of DA neurons) are deficient at reinforcement learning. Treatment with L-DOPA alleviates this.