Biochemical Neuron
BCH 575

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Neuronal Signal Transduction

Neuronal Signal Transduction

- The intracellular signaling begins when extracellular chemical signals (such as neurotransmitters, hormones, and trophic factors) bind to specific receptors located either on the surface or in the cytoplasm or nucleus of the target cells.

- This binding activates the receptors and stimulates cascades of intracellular reactions involving:

GTP-binding proteins, second-messenger molecules, protein kinases, ion channels, and many other effector proteins whose modulation temporarily changes the physiological state of the target cell.

- These same intracellular signal transduction pathways can also cause longer-lasting changes by altering the transcription of genes, thus affecting the protein composition of the target cells on a more permanent basis Intracellular

Importance of signal transduction Causes signal amplification

Amplification guarantees that a physiological response is evoked Permits precise control of cell behavior over a wide range of times.

Some molecular interactions allow information to be transferred rapidly, while others are slower and longer lasting

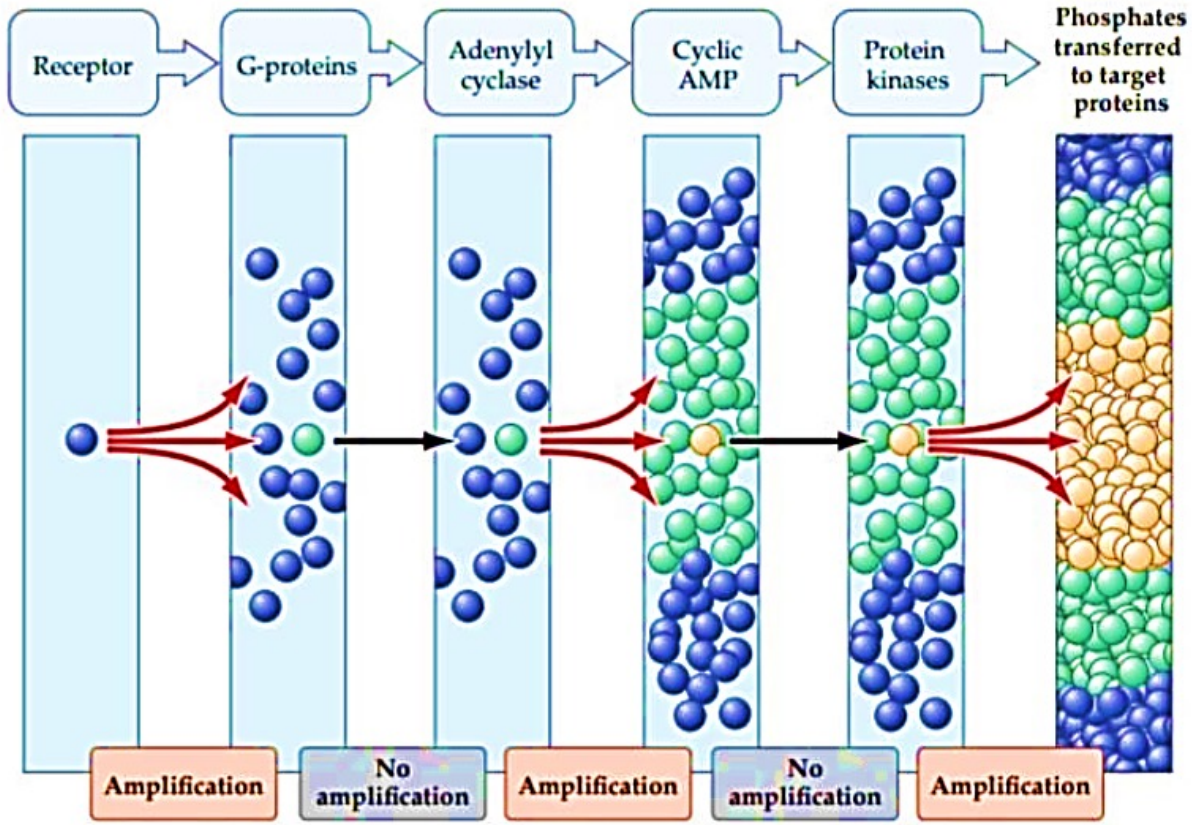


FIGURE 7.2 Amplification in signal transduction pathways. The activation of a single receptor by a signaling molecule, such as the neurotransmitter norepinephrine, can lead to the activation of numerous G-proteins inside cells. These activated proteins can bind to other signaling molecules, such as the enzyme adenylyl cyclase. Each activated enzyme molecule generates a large number of cAMP molecules. cAMP binds to and activates another family of enzymes—the protein kinases—that can phosphorylate many target proteins. Although not every step in this signaling pathway involves amplification, overall the cascade results in a tremendous increase in the potency of the initial signal.

Activation of Signaling Pathways

Chemical signaling molecule that activate intracellular signal transduction pathways can be grouped into three classes:

1. cell impermeant signaling molecules
2. cell-permeant signaling molecules
3. cell-associated signaling molecules

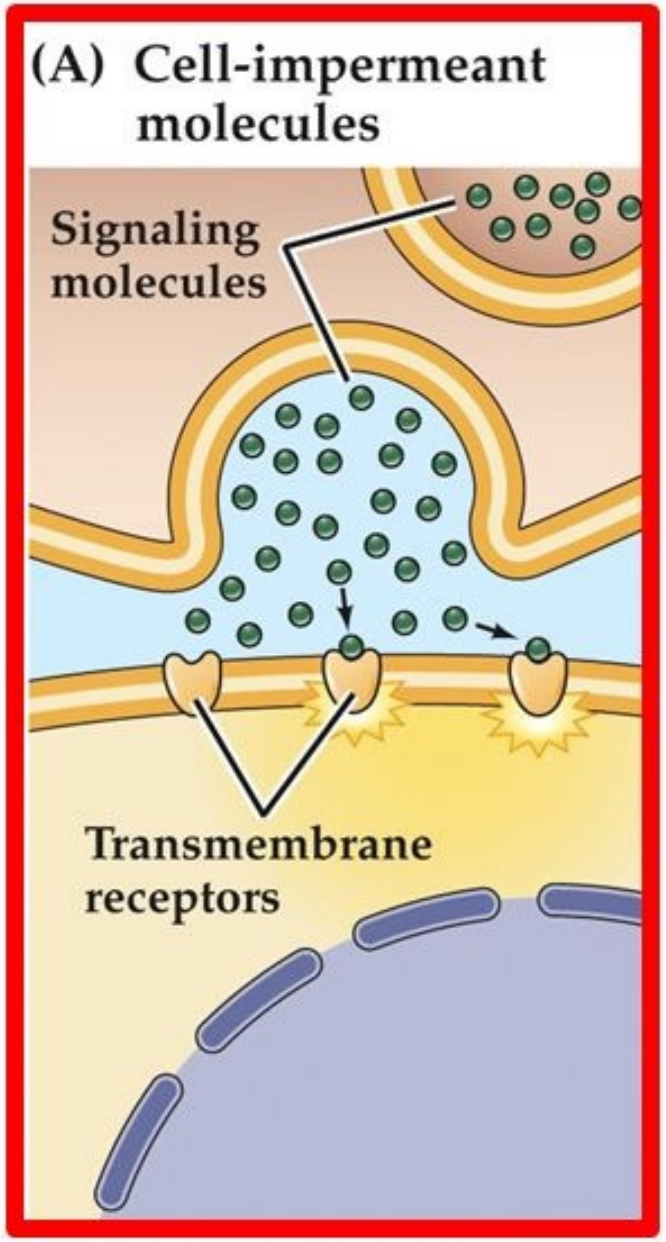
The first two classes are secreted molecules and thus can act on target cells removed from the site of signal synthesis or release.

cell impermeant signaling molecules

Cell-impermeant typically bind to receptors associated with the plasma membrane.

Examples : neurotransmitters; proteins such as neurotrophic factors ; and peptide hormones such as glucagon, insulin, and various reproductive hormones.

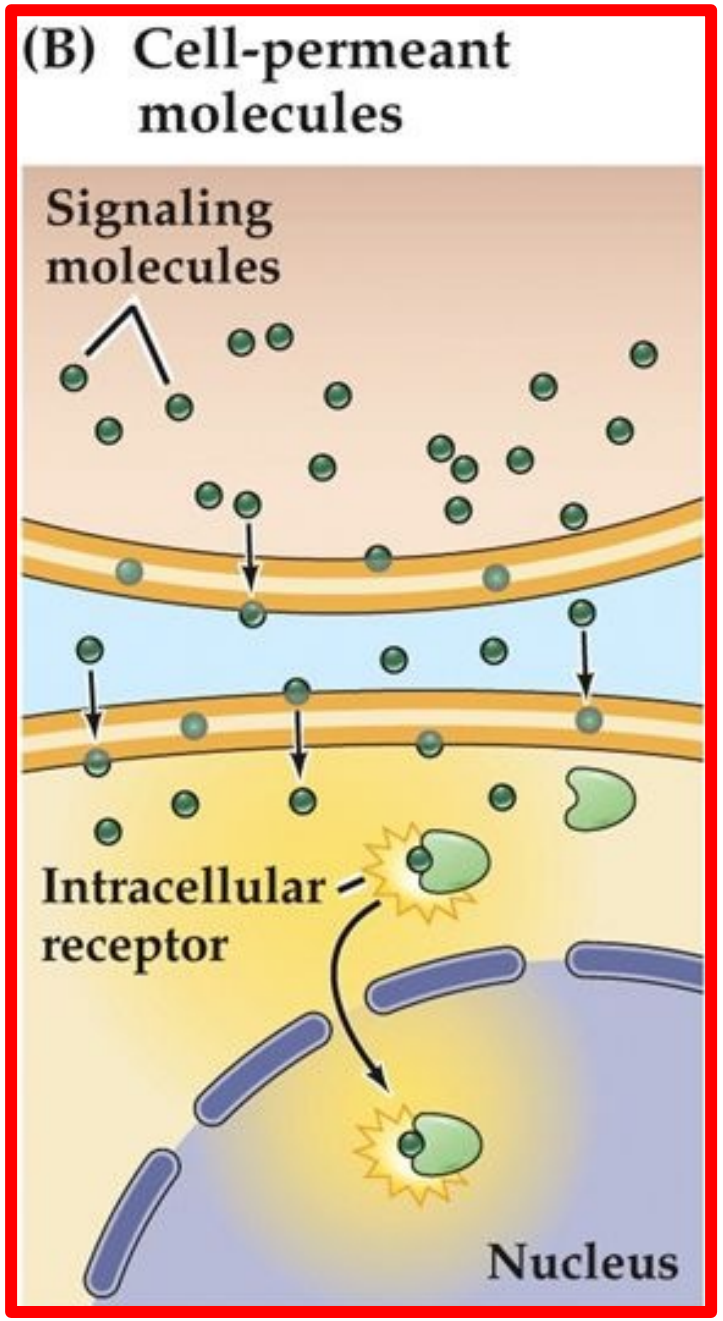
These signaling molecules are typically short-lived, either because they are rapidly metabolized or because they are internalized by endocytosis once bound to their receptors



NEUROSCIENCE 5e, Figure 7.3

Cell-permeant signaling molecules

Cell-permeant signaling molecules can cross the plasma membrane to act directly on receptors that are inside the cell. Examples: numerous steroid hormones (glucocorticoids, estradiol, and testosterone), thyroid hormones (thyroxin), and retinoids. These signaling molecules are relatively insoluble in aqueous solutions and are often transported in blood and other extracellular fluids by binding to specific carrier proteins such as chaperon protein . In this form, they may persist in the bloodstream for hours or even days



NEUROSCIENCE 5e, Figure 7.3

Do you know what is the chaperon protein?

cell-associated signaling molecules

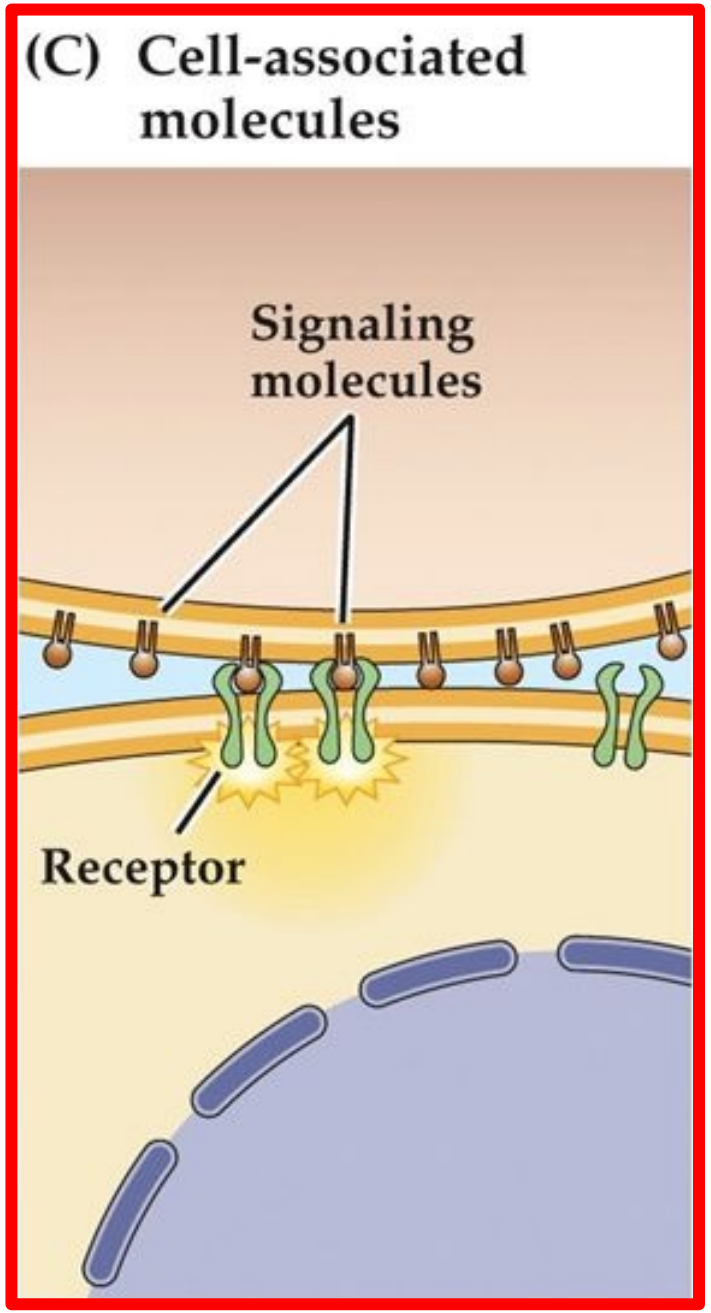
cell-associated signaling molecules are on the extracellular surface of the plasma membrane. these molecules act only on other cells that are physically in contact with the cell that carries such signals.

such as :

1. neural cell adhesion molecules (NCAMs) that influence axonal growth . They are clearly important in neuronal development

2. Integrins and cadherins function not only as cell adhesion molecules but also as signaling molecules that regulate cell proliferation and survival in response to cell-cell and cell-matrix contacts.

How the synaptic adhesion proteins participate in plasticity of synaptic connections?



NEUROSCIENCE 5e, Figure 7.3

Roles of intracellular signal transduction processes in the nervous system

Three important signal transduction pathways can illustrate some of the roles of intracellular signal transduction processes in the nervous system.

1. Nerve growth factor NGF/TrkA

- The first of these is signaling by the **nerve growth factor (NGF) NGF/TrkA.**
- This protein is a member of the neurotrophin growth factor family and is required for the differentiation, survival, and synaptic connectivity of sympathetic and sensory neurons.
- NGF works by binding to a high-affinity tyrosine kinase receptor, TrkA (Protein kinase B (PKB), found on the plasma membrane of these target cells.
- NGF binding causes TrkA receptors to dimerize, and the intrinsic tyrosine kinase activity of each receptor then phosphorylates its partner receptor.
- Phosphorylated TrkA receptors trigger the ras cascade, resulting in the activation of multiple protein kinases.

Therefore, primarily mediates the NGF-dependent survival of sympathetic and sensory neurons

Nerve growth factor NGF/TrkA

- Some of these kinases translocate to the nucleus to activate transcriptional activators, such as cAMP Response Element-Binding Protein (CREB)
- The ras-based component of the NGF pathway is primarily responsible for inducing and maintaining differentiation of NGF-sensitive neurons.
- Also, Phosphorylation of TrkA also causes this receptor to stimulate the activity of phospholipase C, which increases production of IP3 and DAG.
- IP3 induces the release of Ca2+ from the endoplasmic reticulum, and diacylglycerol activates PKC.
- These two second messengers appear to target many of the same downstream effectors as ras.
- Finally, activation of TrkA receptors also causes activation of other protein kinases (such as Akt kinase) that inhibit cell death.

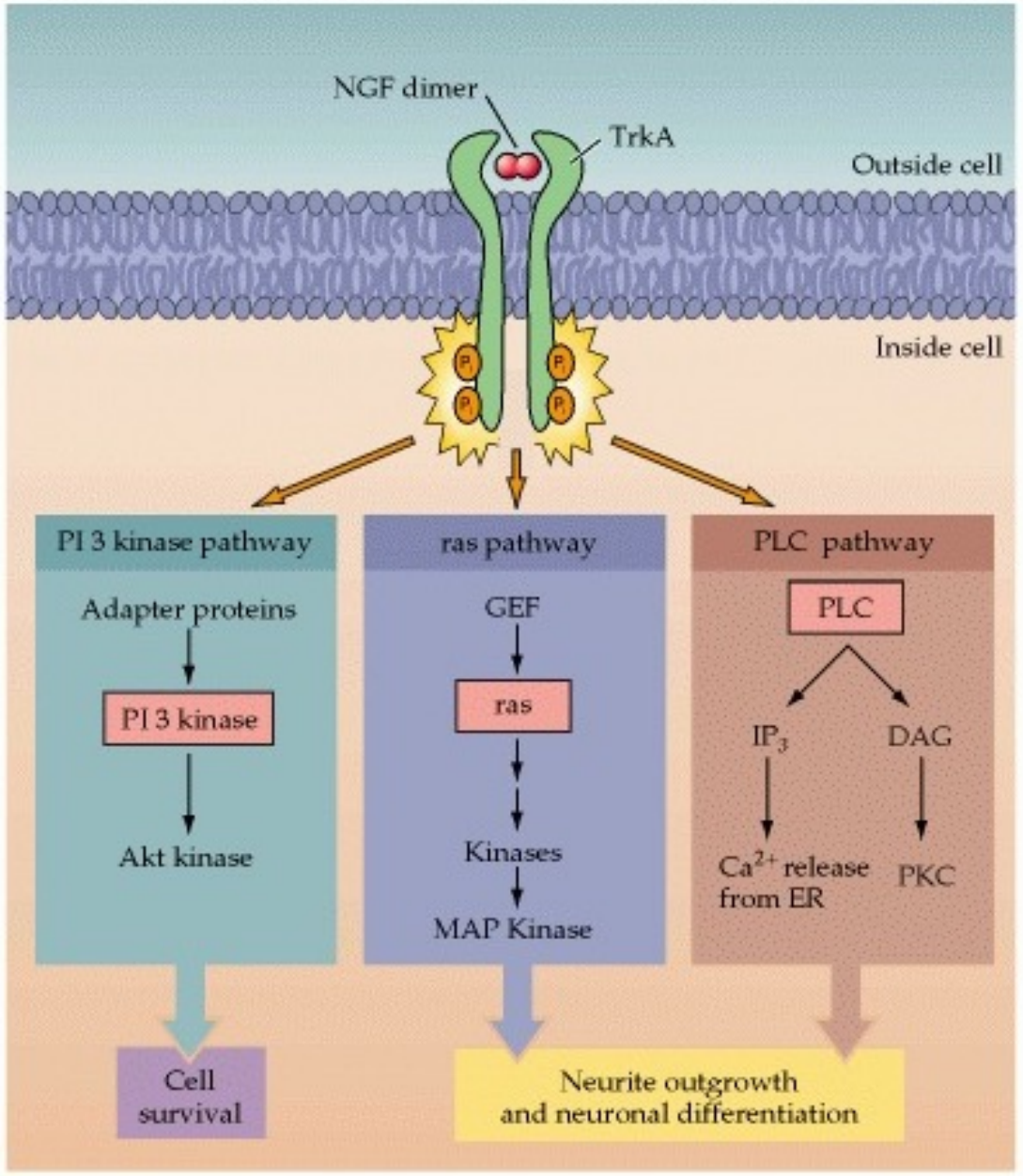
Could you please describe the potential role of IP3/Ca^{2+} signaling and phosphodiesterases in Alzheimer's disease as neurodegeneration disease?

Nerve growth factor NGF/TrkA

Mechanism of action of NGF. NGF binds to a high-affinity tyrosine kinase receptor, TrkA, on the plasma membrane to induce phosphorylation of TrkA at two different tyrosine residues. These phosphorylated tyrosines serve to link various adapter proteins or phospholipase C (PLC), which, in turn, activate three major signaling pathways:

the PI 3 kinase pathway leading to activation of Akt kinase,

the ras pathway leading to MAP kinases(A mitogen-activated protein kinase), and the PLC pathway leading to release of intracellular Ca^{2+} and activation of PKC. The ras and PLC pathways primarily stimulate processes responsible for neuronal differentiation, while the PI 3 kinase pathway is primarily involved in cell survival.



Please discrip the role of Nerve growth factor NGF/TrkA through ras affacted signaling pathway in neuronal differentation?

CREB and schizophrenia.

The cAMP-response element binding protein (CREB) is an intracellular protein that regulates the expression of genes that are important in dopaminergic neurons.

Dopamine is a brain neurotransmitter involved in the pathology of schizophrenia. The dopamine hypothesis states that, in schizophrenia, dopaminergic signal transduction is hyperactive.

Dopamine affects the phosphorylation of CREB via G protein-coupled receptors. Neurotrophins, such as brain derived growth factor (BDNF), are critical regulators during neurodevelopment and synaptic plasticity.

The CREB is one of the major regulators of neurotrophin responses since phosphorylated CREB binds to a specific sequence in the promoter of brain derived growth factor (BDNF) and regulates its transcription.
Abnormalities of CREB expression is observed in the brain of individuals suffering from schizophrenia.

Dopamine-Mediated Signaling Affects the Activity of CREB

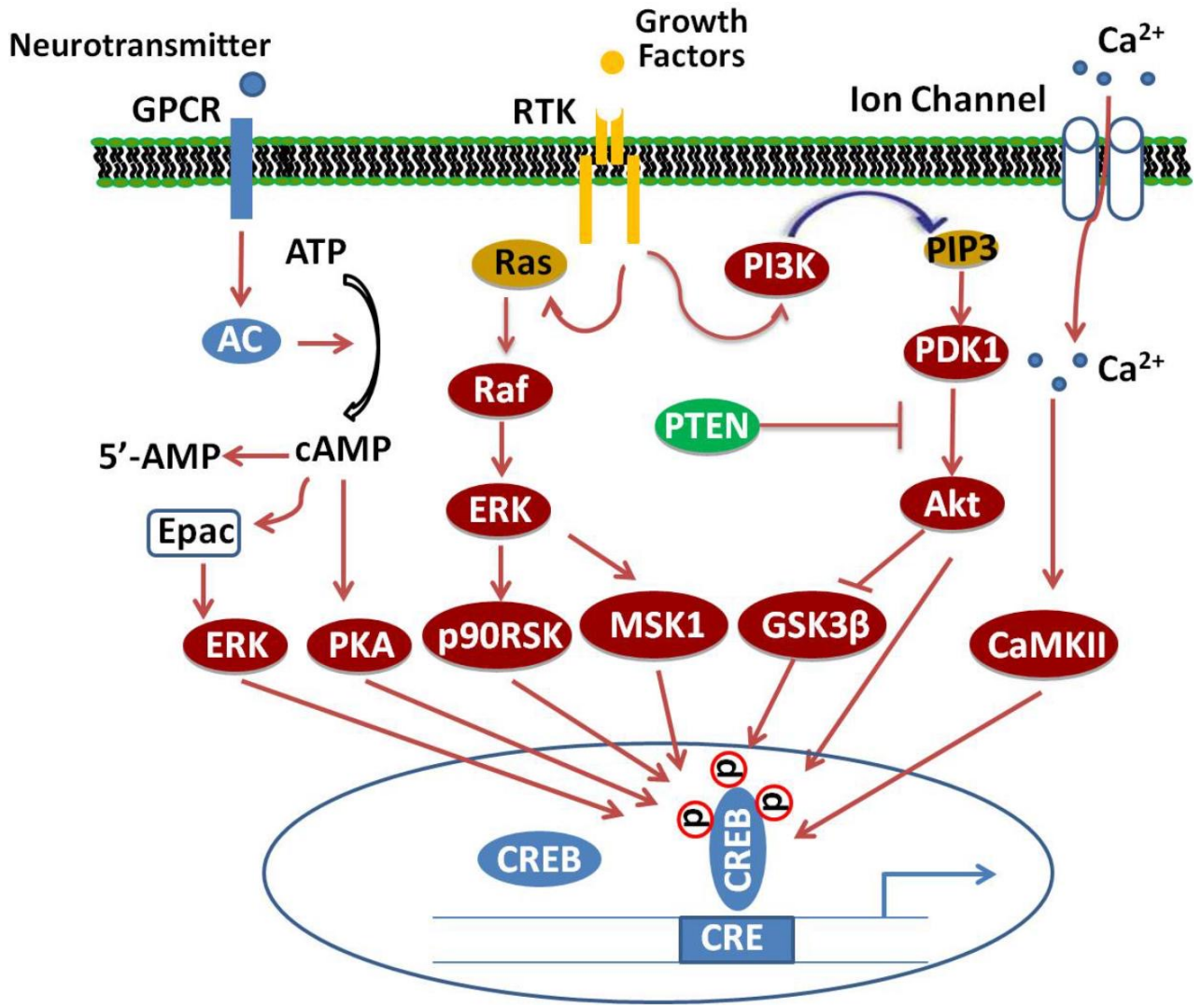
Binding of dopamine to its receptors enhances the phosphorylation of CREB through multiple pathways:

1. Binding of dopamine to D1R elevates intracellular cAMP levels and activates PKA followed by the phosphorylation of CREB.
2. Binding of dopamine to D2R reduces cAMP production and adenylate cyclase activity followed by reduced phosphorylation of CREB.

3. D2R is also coupled to phospholipase Cβ (PLCβ). Activation of D2R by its agonist quinpirole causes an elevation of intracellular Ca^{2+} and activation of PKC. The Ca^{2+}/CaMK and PKC are the upstream protein kinases phosphorylating CREB and, therefore, enhanced Ca^{2+} and activation of PKC cause the phosphorylation and activation of CREB
4. Stimulation of D1R and D2R with agonists activates Akt kinase, which translocates to the nucleus. Activated Akt directly phosphorylates CREB at Ser133 in neurons
5. CREB stimulates the expression of a number of genes containing CREs (5′-TGACGTCA-3′) in their promoter regions which may be associated with schizophrenia such as D1R, serotonin transporter, and synapsin 1. It has been also reported that D1R/D2R plays a synergistic role in inducing CREB–DNA binding activities

Signaling Cascades Regulating the Activity of CREB

- Signaling cascade of CREB. Adenylate cyclase (AC) activated upon stimulation of cellular G-protein-coupled receptors (GPCR) by neurotransmitters increases cAMP levels, which, in turn, activate PKA.
- The catalytic subunits of PKA translocate into the nucleus and phosphorylate CREB at Ser133. Binding of growth factors to receptor tyrosine kinases (RTK) stimulate the activation of PI3K/Akt/GSK3β, Ras/Raf/MEK/ERK/p90/RSK and ERK/MSK1 signaling pathways, which subsequently enhance the phosphorylation of CREB at different sites.
- Additionally, activation of excitatory NMDA receptors will increase the phosphorylation of CREB through Ca^{2+}/CaMK-dependent pathways.



Long-term depression (LTD)

- Long-term depression (LTD). Another example of intracellular signaling can be observed during synaptic transmission between parallel fibers and Purkinje cells in the cerebellum.
- This synapse is central to information flow through the cerebellar cortex, which in turn helps coordinate motor movements.
- When parallel fibers are active, they release the neurotransmitter glutamate onto the dendrites of their Purkinje cell targets.
- This activates AMPA-type receptors, which are ligand-gated ion channels, causing a small inward current that depolarizes the Purkinje cell for a few milliseconds.
- Ca2+ concentration in the dendrites until the IP3 is metabolized and the Ca2+ is pumped out of the cytoplasm.

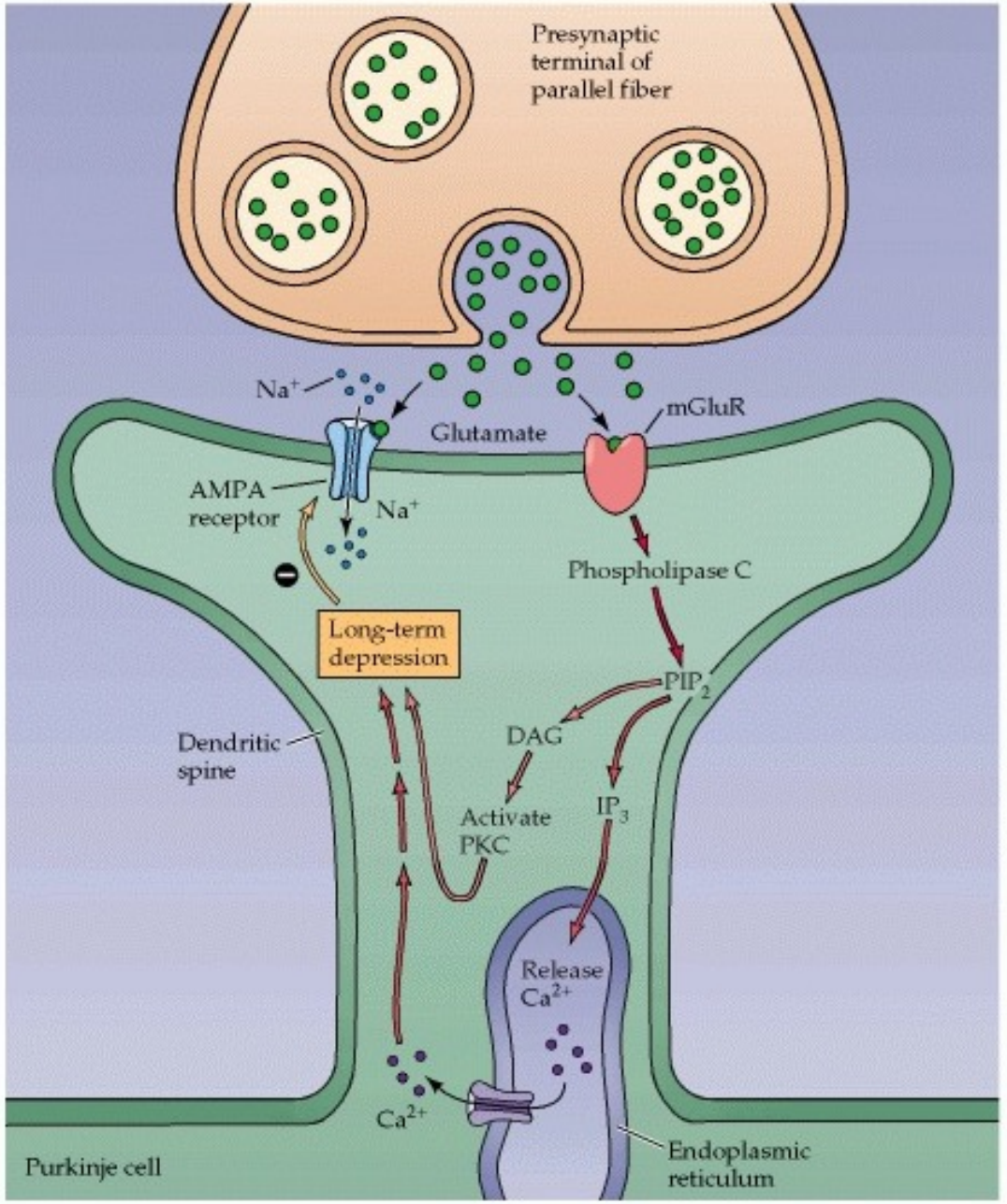
- In addition to this electrical signal, parallel fiber transmission also generates two postsynaptic second messengers.
- The glutamate released by parallel fibers activates metabotropic glutamate receptors, which are G-protein-linked receptors that cause activation of phospholipase C.
- This enzyme produces IP3 and DAG within the Purkinje cell.
- The IP3 causes Ca2+ to be released from the endoplasmic reticulum, transiently elevating cytoplasmic
- Given appropriate patterns of electrical activity, the calcium released by IP3 can produce long-term depression (LTD), a form of synaptic plasticity that causes the parallel fiber synapses to become less effective
- One possibility is that Ca2+ activates protein kinase C, which is also activated by the DAG that is produced in Purkinje cells by parallel fibers. Thus, these two messengers may converge on PKC, which then phosphorylates an unknown substrate.
- Ultimately, these signaling processes change the postsynaptic, AMPA-type glutamate receptors, so that these receptors produce smaller electrical signals in response to the glutamate released from the parallel fibers. This weakening of the parallel fiber synapse is the final cause of LTD.

In summary, parallel fiber synaptic transmission produces brief electrical signals and chemical signals that last much longer. The actions of IP3 and DAG also are restricted to small parts of the Purkinje cell dendrite, which is a more limited spatial range than the parallel fiber EPSP, which spreads throughout the entire dendrite and cell body of the Purkinje cell.

Thus, in contrast to the electrical signals, the second messenger signals can impart precise information about the location of active synapses, potentially influencing synapses in the vicinity of active parallel fibers.

Signaling at cerebellar parallel fiber synapses

Glutamate released by parallel fibers activates both AMPA-type(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and metabotropic receptors. The latter produces IP3 and DAG within the Purkinje cell. The IP3 causes Ca2+ to be released from the endoplasmic reticulum, while DAG activates protein kinase C. These signals together change the properties of AMPA receptors to produce LTD.



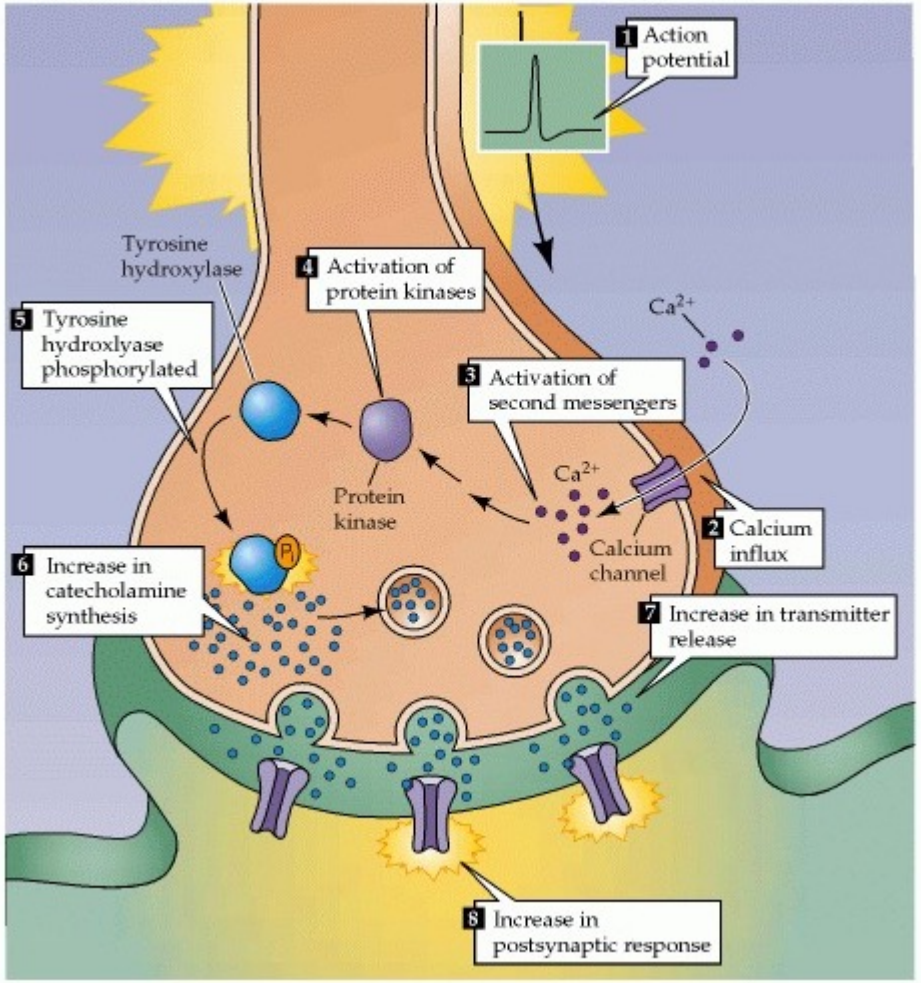
Phosphorylation of tyrosine hydroxylase

•Phosphorylation of tyrosine hydroxylase. Third intracellular signaling in the nervous system is the regulation of the enzyme tyrosine hydroxylase.

• Tyrosine hydroxylase governs the synthesis of the **catecholamine neurotransmitters: dopamine, norepinephrine, and epinephrine.**

•A number of signals, including electrical activity, other neurotransmitters, and NGF, increase the rate of catecholamine synthesis by increasing the catalytic activity of tyrosine hydroxylase.

•The rapid increase of tyrosine hydroxylase activity is largely due to the phosphorylation of this enzyme.

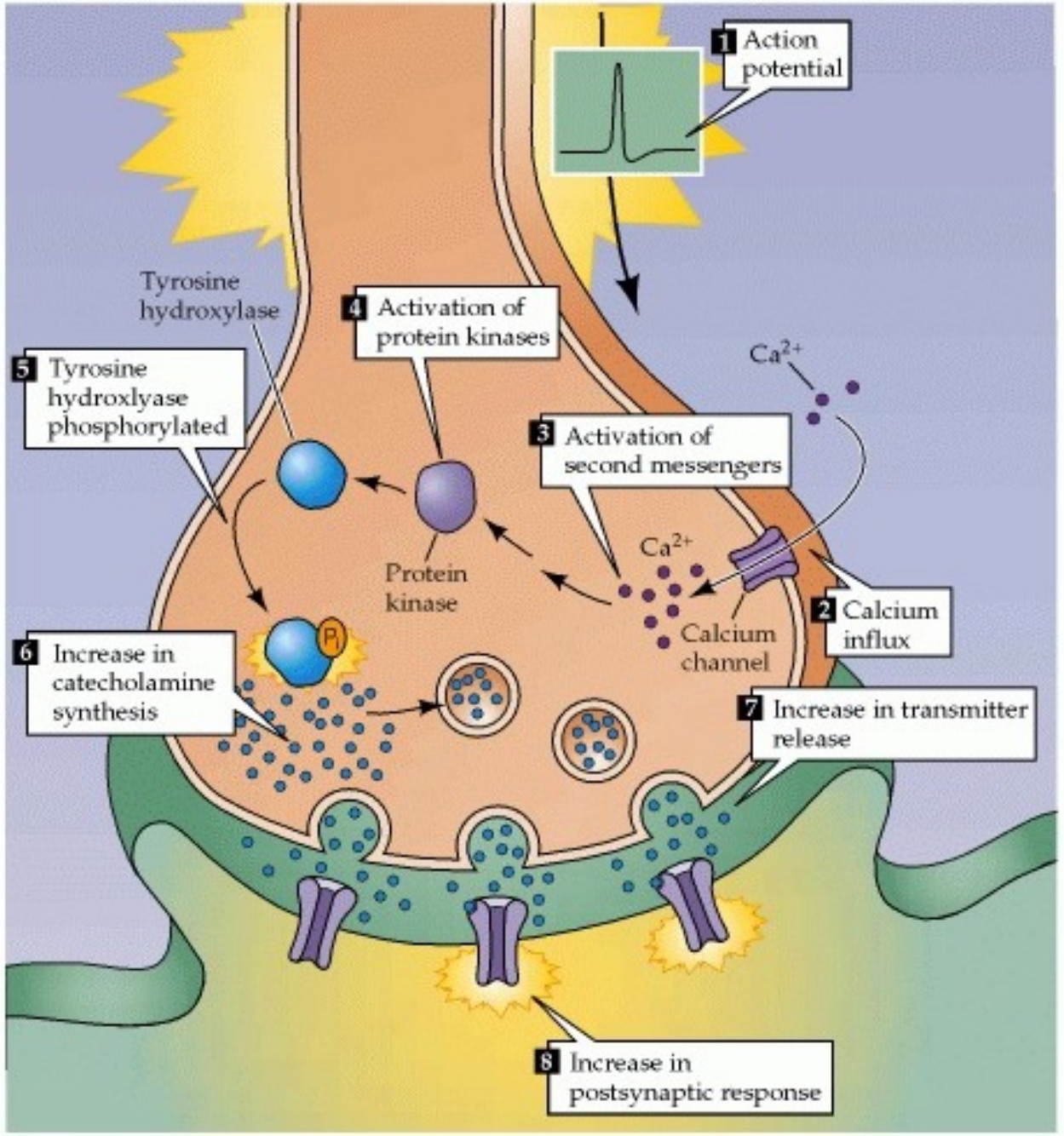


Regulation of tyrosine hydroxylase by protein phosphorylation. This enzyme governs the synthesis of the catecholamine neurotransmitters and is stimulated by a number of intracellular signals. In the example shown here, neuronal electrical activity (1) causes an influx of Ca^{2+} (2). The resultant rise in intracellular Ca^{2+} concentration (3) activates protein kinases (4), which phosphorylates tyrosine hydroxylase (5) to stimulate catecholamine synthesis (6). This, in turn, increases the release of catecholamines (7) and enhances the postsynaptic response produced by the synapse (8).

Tyrosine hydroxylase is a substrate for several protein kinases, including PKA, CaMKII, MAP kinase, and PKC. Phosphorylation causes conformational changes that increase the catalytic activity of tyrosine hydroxylase.

Stimuli that elevate cAMP, Ca2+, or DAG can all increase tyrosine hydroxylase activity and thus increase the rate of catecholamine biosynthesis.

This regulation by several different signals allows for close control of tyrosine hydroxylase activity and illustrates how several different pathways can converge to influence a key enzyme involved in synaptic transmission.



Regarding your study of neuron signal transduction, please illustrate the following paper as ppt (Signal Transduction in the brain)?

file:///C:/Users/aalkh/Downloads/CHAPTER%204_%20Signal%20Transduction%20in%20the%20Brain.pdf