

Modulation of Peripheral Sensitization

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Peripheral sensitization is the reduction in the threshold of excitability of sensory neurons that results in an augmented response to a given external stimulus. Sensitization can be mediated by post-translational events that alter the activity of ion channels and other proteins and/or by alterations in gene expression that lead to a change in the phenotype of the neuron. Peripheral sensitization increases the amount of neurotransmitter released from peripheral endings of small diameter sensory neurons and from terminals in the dorsal spinal cord, which augments neurogenic inflammation and pain perception.

Excitatory Mechanisms

Noxious stimuli can excite the peripheral endings of primary sensory afferents, giving rise to activation of voltage-gated ion channels and/or ligand-gated receptors that lead to the generation of action potentials. The best characterized ligand-gated receptor/channel complex is the transient receptor potential cation channel, subfamily V, member 1 (TRPV1), which is activated by capsaicin, low pH, heat, and endovanilloids. The activity of both voltage-gated and ligand-gated channels can be modulated by intracellular signaling pathways so that for any given stimulus, the number of evoked action potentials can be enhanced. This process which is known as sensitization can result in an increase in transmitter release from the endings of sensory neurons thereby augmenting neurogenic inflammation and/or nociception.

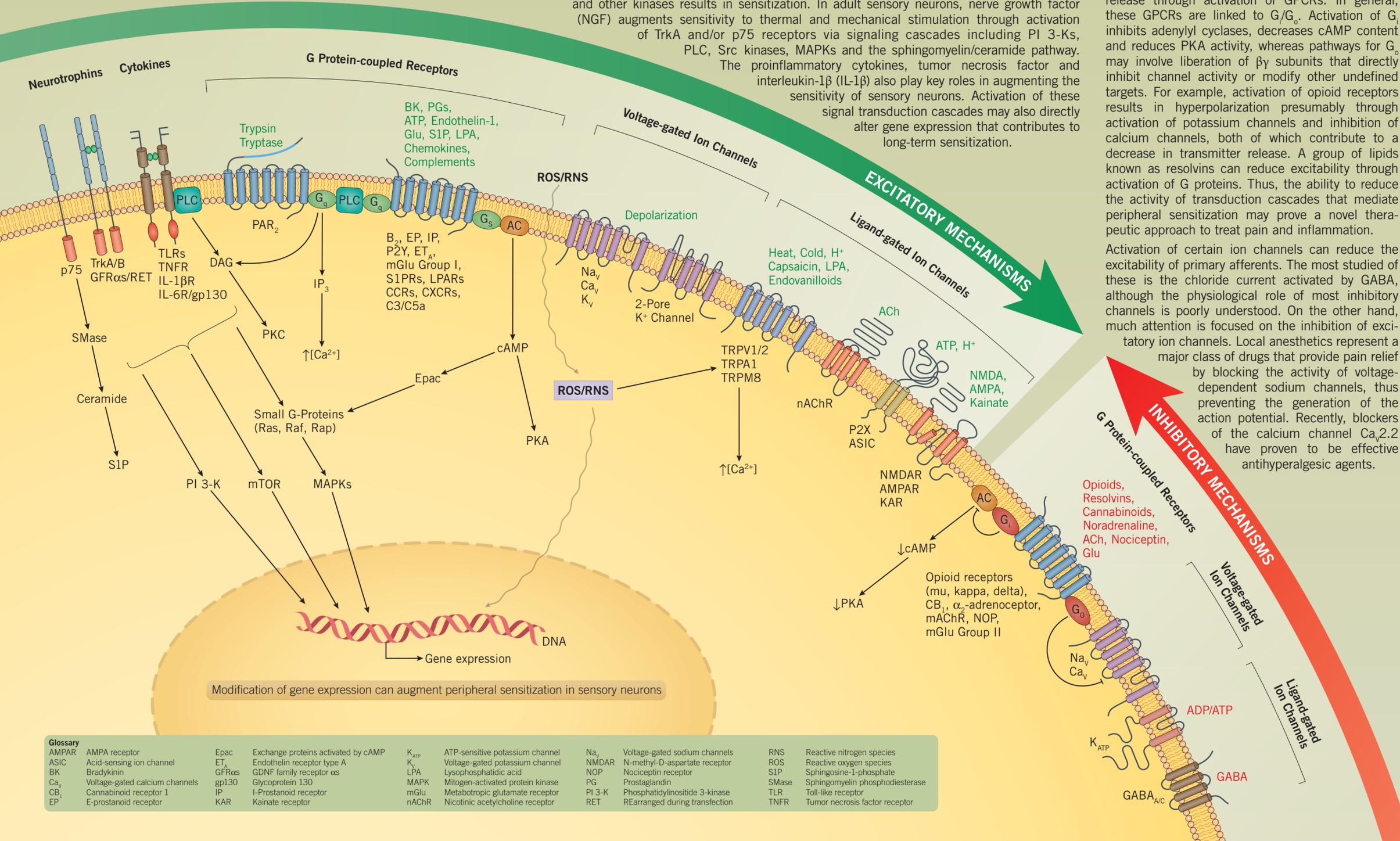
Activation of G protein-coupled receptors (GPCRs) by molecules such as prostaglandins, bradykinin, chemokines, sphingolipids, and other lipids also increases the excitability of sensory neurons. Proteinase-activated receptors (PARs) which are activated by enzymatic cleavage of the extracellular N-terminal sequence of the GPCR also enhance excitability. In general, GPCRs are linked to G_s which, through cAMP, activates protein kinase A (PKA) or Epacs; or to G_q/G_{11} families, which activate phospholipase C (PLC) to increase intracellular calcium and activate protein kinase C (PKC) isozymes. G protein $\beta\gamma$ subunits also activate a number of downstream signaling cascades including PI 3-Ks and MAPKs which can sensitize sensory neurons.

Phosphorylation of a number of target proteins including ion channels, synaptic proteins, and other kinases results in sensitization. In adult sensory neurons, nerve growth factor (NGF) augments sensitivity to thermal and mechanical stimulation through activation of TrkA and/or p75 receptors via signaling cascades including PI 3-Ks, PLC, Src kinases, MAPKs and the sphingomyelin/ceramide pathway. The proinflammatory cytokines, tumor necrosis factor and interleukin- 1β (IL- 1β) also play key roles in augmenting the sensitivity of sensory neurons. Activation of these signal transduction cascades may also directly alter gene expression that contributes to long-term sensitization.

Inhibitory Mechanisms

The ability to diminish peripheral sensitization is an important strategy for the development of drugs to treat pain and inflammation. Two approaches have been used in most recent drug development: 1) block the sensitizing actions of proinflammatory agents through synthesis blockers, receptor antagonists, or neutralizing agents (antibodies or pseudoreceptor); and 2) reduce excitability through a direct action on inhibitory pathways. A number of antinociceptive agents reduce excitability and inhibit transmitter release through activation of GPCRs. In general, these GPCRs are linked to G_i/G_o . Activation of G_i inhibits adenylyl cyclases, decreases cAMP content and reduces PKA activity, whereas pathways for G_o may involve liberation of $\beta\gamma$ subunits that directly inhibit channel activity or modify other undefined targets. For example, activation of opioid receptors results in hyperpolarization presumably through activation of potassium channels and inhibition of calcium channels, both of which contribute to a decrease in transmitter release. A group of lipids known as resolvins can reduce excitability through activation of G proteins. Thus, the ability to reduce the activity of transduction cascades that mediate peripheral sensitization may prove a novel therapeutic approach to treat pain and inflammation.

Activation of certain ion channels can reduce the excitability of primary afferents. The most studied of these is the chloride current activated by GABA, although the physiological role of most inhibitory channels is poorly understood. On the other hand, much attention is focused on the inhibition of excitatory ion channels. Local anesthetics represent a major class of drugs that provide pain relief by blocking the activity of voltage-dependent sodium channels, thus preventing the generation of the action potential. Recently, blockers of the calcium channel $Ca_v2.2$ have proven to be effective antihyperalgesic agents.



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EXCITATORY MECHANISMS

G-Protein-coupled Receptors

Bradykinin Receptors: Bradykinin, HOE 140

Endothelin-1 Receptors: BQ-123, BQ 788

mGlu Receptors: CGP 55845, DCG IV, LY 341495, (S)-MCPG, MNI-caged-L-glutamate

PAR₂ Tachykinin Receptors: FSLRLRY-NH₂, SLIGKV-NH₂, GR 159897, RP 67580

Intracellular Targets

Epac: 8CPT-2Me-cAMP, HJC 0350, 8-pCPT-2-O-Me-cAMP-AM

S1P: CYM 50308, CYM 5442

Ligand-gated Ion Channels

ASICs: APETx2, Psalmotoxin 1

nACh Receptors: α-Bungarotoxin, Dihydro-β-erythroidine, Methyllycaconitine citrate, PNU 120596, Varenicline tartrate

P2X Receptors: A 804598, NF 449, Ro 51

TRP Channels: A 784168, AMG 9810, AMTB, Capsazepine, HC 030031, Icilin

Neurotrophins

RET: SU 5416, Sunitinib

Trk Receptors: ANA 12, 7,8-Dihydroxyflavone, GW 441756

Voltage-gated Ion Channels

Ca_v Channels: (±)-Bay K 8644, ω-Conotoxin GVIA, Mibefradil, Pregabalin

K_{ATP} Channels: BL 1249

Na_v Channels: A 887826, Huwentoxin IV, PF 04885614, Tetrodotoxin citrate, Veratridine

Inhibitory Mechanisms

G-Protein-coupled Receptors

Cannabinoid Receptors: AM 251, 2-Arachidonylglycerol, JWH 133

GABA_B: CGP 55845, SCH 50911, SKF 97541

Opioid Receptors: AR-M 1000390, nor-Binaltorphimine, CTOP, DAMGO, (±)-J 113397, SCH 221510, SNC 80, (±)-U-50488

Ligand-gated Ion Channels

GABA_A Receptors: (+)-Bicuculline, RuBi GABA trimethylphosphine, SR 95531

Voltage-gated Ion Channels

K_{ATP} Channels: Glibenclamide, Levromakalim, Nateglinide

K_v Channels: ICA 069673, NS 5806, XE 991

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Glossary

AMPA: AMPA receptor
ASIC: Acid-sensing ion channel
BK: Bradykinin
Ca_v: Voltage-gated calcium channels
CB₁: Cannabinoid receptor 1
EP: E-prostanoid receptor

Epac: Exchange proteins activated by cAMP
ET_A: Endothelin receptor type A
GFRαs: GDNF family receptor αs
gp130: Glycoprotein 130
IP: I-Prostanoid receptor
KAR: Kainate receptor

K_{ATP}: ATP-sensitive potassium channel
K_v: Voltage-gated potassium channel
LPA: Lysophosphatidic acid
MAPK: Mitogen-activated protein kinase
mGlu: Metabotropic glutamate receptor
nAChR: Nicotinic acetylcholine receptor

Na_v: Voltage-gated sodium channels
NMDAR: N-methyl-D-aspartate receptor
NOP: Nociceptin receptor
PG: Prostaglandin
PI 3-K: Phosphatidylinositolide 3-kinase
RET: REarranged during transfection

RNS: Reactive nitrogen species
ROS: Reactive oxygen species
S1P: Sphingosine-1-phosphate
SMase: Sphingomyelin phosphodiesterase
TLR: Toll-like receptor
TNFR: Tumor necrosis factor receptor

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