Modulation of Peripheral Sensitization

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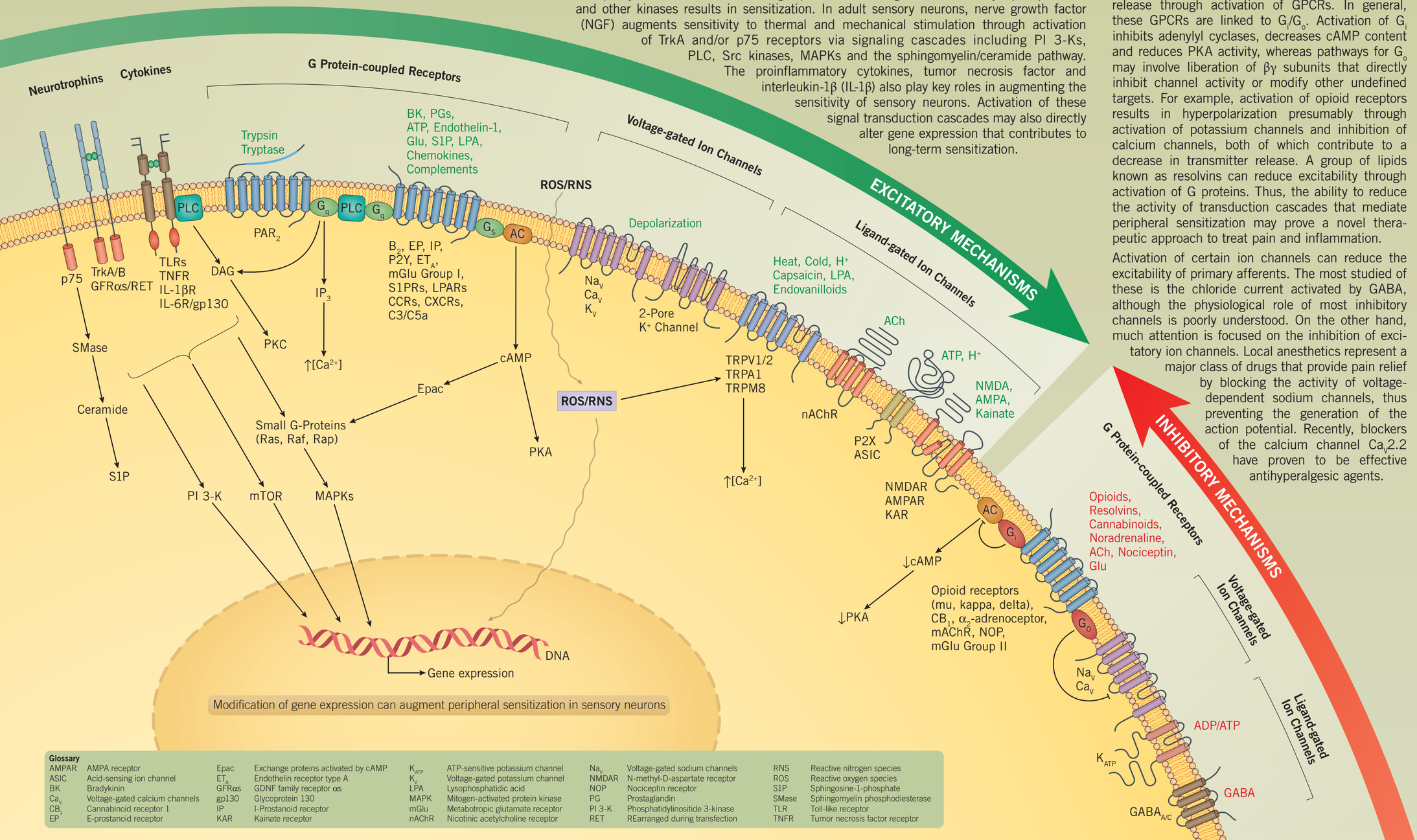
Peripheral sensitization is the reduction in the threshold of excitability of sensory neurons that results in an augmented response to a given external stimulus. Sensitization can be mediated by post-translational events that alter the activity of ion channels and other proteins and/or by alterations 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 βγ 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.



Glossary

AMPAR	AMPA receptor	Epac	Exchange proteins activated by cAMP	K_{ATP}	ATP-sensitive potassium channel	Na_V	Voltage-gated sodium channels	RNS	Reactive nitrogen species
ASIC	Acid-sensing ion channel	ET_A	Endothelin receptor type A	K_V	Voltage-gated potassium channel	NMDAR	N-methyl-D-aspartate receptor	ROS	Reactive oxygen species
BK	Bradykinin	GFRαs	GDNF family receptor αs	LPA	Lysophosphatidic acid	NOP	Nociceptin receptor	S1P	Sphingosine-1-phosphate
Ca_V	Voltage-gated calcium channels	gp130	Glycoprotein 130	MAPK	Mitogen-activated protein kinase	PG	Prostaglandin	SMase	Sphingomyelin phosphodiesterase
CB_1	Cannabinoid receptor 1	IP	I-Prostanoid receptor	mGlu	Metabotropic glutamate receptor	PI 3-K	Phosphatidylinositide 3-kinase	TLR	Toll-like receptor
EP	E-prostanoid receptor	KAR	Kainate receptor	nAChR	Nicotinic acetylcholine receptor	RET	REarranged during transfection	TNFR	Tumor necrosis factor receptor

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 βγ 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
PAR_2	FSLLRY-NH2, SLIGKV-NH2
Tachykinin Receptors	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_{2P} 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, Levcromakalim, Nateglinide
K_V Channels	ICA 069673, NS 5806, XE 991

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