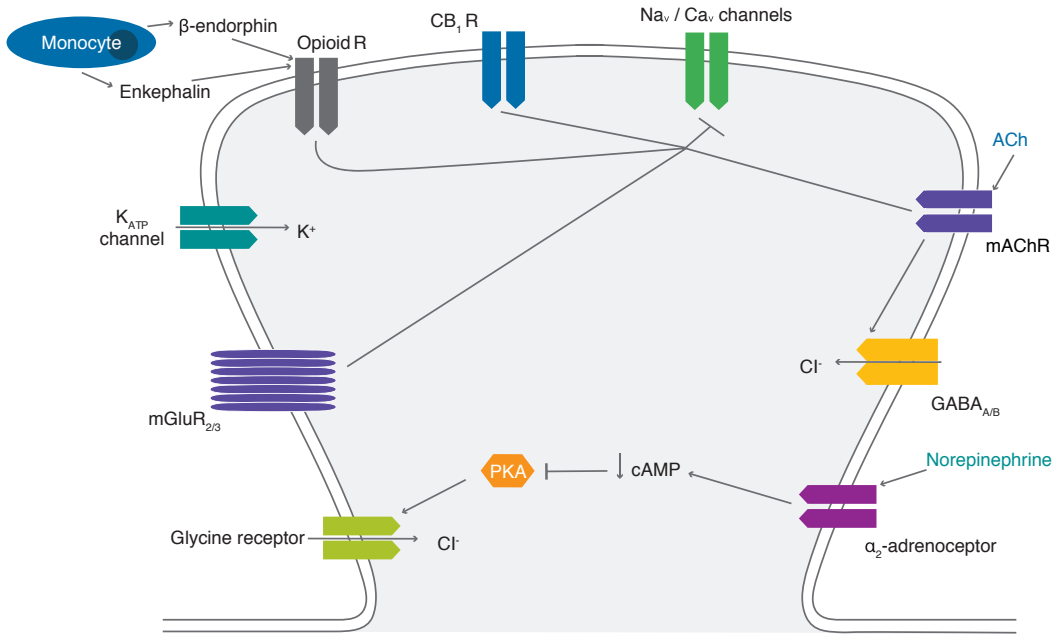
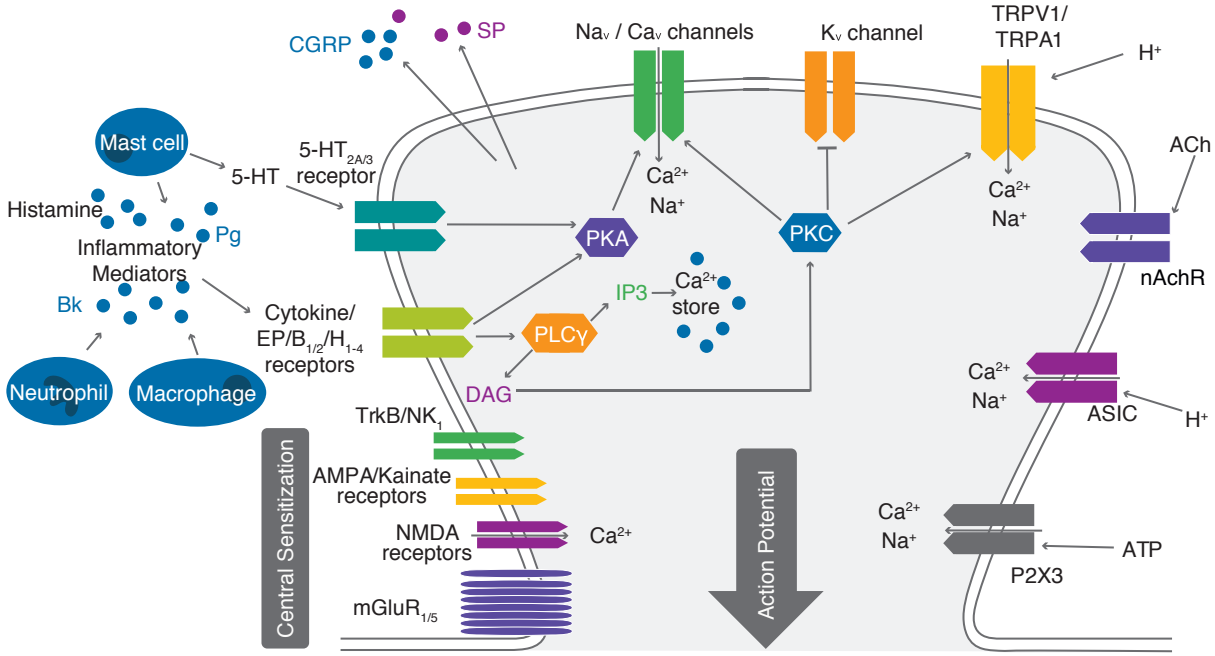
Signaling Pathways in Pain

Peripheral Nociceptor Inhibition



Peripheral Nociceptor Excitation



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Signaling Pathways in Pain

The sensation of pain can be separated into neuropathic, inflammatory and nociceptive pain which are stimulated by heat, acid, mechanical pressure and cold. It involves a complex interplay of peripheral sensitization, central sensitization and inhibition.

Signaling Pathways in Peripheral Pain Sensitization

The activation of receptors and channels at afferent nociceptor Aδ and C fibre terminals leads to the generation of an action potential that travels up the spinal cord to the brain for conscious pain perception. ASIC, TRPA1 and TRPV1 channels open in response to a decrease in pH and H^+ binding, leading to Ca^{2+} and Na^+ influx.

Inflammatory mediators produced by damaged cells and immune cells activate prostaglandin EP, bradykinin $B_{1/2}$ and cytokine receptors. Serotonin and ATP activate 5-$HT_{2A/3}$ receptor and P2X3 receptors respectively. Activation of these receptors activates ERK, p38, PKA, PLC and PKC causing release of intracellular Ca^{2+}. These enzymes also increase Ca^{2+} and Na^+ influx and inhibit K^+ influx.

Inflammatory mediators can cause peripheral sensitization where innocuous stimuli is experienced as painful. There is increased gene translation and trafficking of ion channels and receptors, with a lowered activation threshold of the TRPV1 channel due to PKC phosphorylation.

There is also central sensitization of pain mediated by glutamate receptors and disinhibition via loss of GABA and glycine inhibition.

Signaling Pathways in Pain Inhibition

Inhibition of peripheral pain is mediated by several receptors such as GABA and glycine receptors which are expressed on afferent neurons pre-synaptically or on dorsal horn neurons post-synaptically. Activation of these receptors decreases the response to noxious stimuli through an influx of Cl^-. Activation of α_2-adrenoceptors by noradrenaline decreases cAMP and inhibits PKA, increasing glycine receptor activity.

Dorsal horn neurons can express mAChRs which are agonised by acetylcholine, inhibiting nociception. Opioid receptors are also expressed, responding to endogenous enkephalin and β-endorphin produced by monocytes. Opioid, CB_1 and $mGlu_{2/3}$ receptors inhibit Ca^{2+} and Na^+ channels and activate K^+ channels.

Example modulators of nociception

CAT NO.	PRODUCT NAME	TARGET
HB1179	(E)-Capsaicin	TRPV1 channel agonist
HB1040	Capsazepine	TRPV1 channel antagonist
HB1185	Resiniferatoxin	Potent TRPV1 channel agonist
HB1201	Tranilast	TRPV2 channel inhibitor. Potent mast cell stabilizer
HB1198	SB 366791	Potent, selective TRPV1 channel antagonist
HB1087	Terfenadine	H_1 receptor antagonist
HB1074	Astemizole	Potent histamine H_1 receptor antagonist
HB0225	D-AP5	Competitive NMDA receptor antagonist
HB0443	NBQX disodium salt	Potent, selective, competitive AMPA receptor antagonist. Disodium salt
HB0901	SR 95531 hydrobromide	Potent, selective, competitive $GABA_A$ receptor antagonist
HB0893	(-)-Bicuculline methiodide	Competitive $GABA_A$ receptor antagonist
HB0960	CGP 55845 hydrochloride	Potent, selective $GABA_B$ receptor antagonist
HB1030	QX 314 chloride	Membrane impermeable Na^+ channel blocker
HB0548	Riluzole hydrochloride	Na^+ channel blocker / glutamate inhibitor
HB1152	ZD 7288	Selective HCN channel blocker
HB1212	ω-Agatoxin IVA	Potent, selective P-type / Q-type Ca^{2+} channel blocker
HB0385	Loperamide hydrochloride	Potent, selective μ-opioid receptor agonist
HB0370	L-AP4	Potent, selective mGlu group III agonist

References

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