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Review Article

PAIN AND PAIN RECEPTORS

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ABSTRACT

Pain results from the complex processing of neural signals at different levels of the central nervous system. Pain messages are picked up by receptors, called nociceptors, and transmitted to the spinal cord via small myelinated fibers and very small unmyelinated fibers. From the spinal cord, the impulses are carried to the brainstem, thalamus, and cerebral cortex and ultimately perceived as pain. A logical strategy for developing novel analgesics is to target the beginning of the pain pathway, and aim potential treatments directly at the nociceptors. A lot of reviews have talked ample about opioid receptors, NMDA receptors, Purinergic receptors, glutamate receptors, cannabinoid receptors and transient receptor potential (TRP) channels and their role in physiology of pain. This review summarizes and focuses on the current progress in our understanding of pain, and pain receptors (nociceptors), their mechanisms along with the various agonists and antagonists available at each receptor; which may help in the discovery of novel classes of drugs and expand our repertoire of targets for pain pharmacotherapy.

Key Words: Nociceptors, Mechanisms, Agonists, Antagonists.

INTRODUCTION

Pain is an unpleasant sensory and emotional experience often caused by intense or damaging stimulus [1]. It is a protective mechanism for the body and causes a human or animal to react to remove the pain stimulus. Enormous strides have been made in understanding the neurophysiology and neurochemistry of transmission and modulation of information about noxious events [2,3] and much also is known about acute inflammation, which commonly drives these neural processes [4]. In contrast, relatively little is known about the pathophysiology underlying most persistent pain syndromes. Nonetheless, it is now widely accepted that persistent pain may be sustained by different types of mechanisms and clinical characteristics can be used to broadly divide pain syndromes into nociceptive, neuropathic, psychogenic or idiopathic.

Nociceptive Pain and Its Mechanisms

If pain is due to ongoing activation of the nociceptive system by tissue injury then it is clinically called nociceptive pain. Nociceptive pain is presumed to occur as a result of the activation of the sensory system by noxious stimuli, a process that involves transduction, transmission, modulation and perception. Tissue injury activates primary afferent neurons called nociceptors, which are small diameter afferent neurons (with A-delta and C-fibers) that respond to noxious stimuli and are found in skin, muscle, joints, and some visceral tissues [2]. These fibers have specific receptors that may be responsible for noxious mechanical, chemical or thermal stimuli. Presumably, nociceptive processes linked to noxious events involving somatic or visceral structures begin with activation of these specific receptors, which leads to transduction, the process by which exposure to a sufficient stimulus produces depolarization of the peripheral nerve. Once depolarization occurs, transmission of information proceeds proximally along the axon to the spinal cord and then on to higher centers. The neuroanatomy, neurophysiology and neurochemistry of these processes are very complex [5]. Transmission across the first central synapse may be influenced by activity in the primary afferent itself and modulatory neural pathways that originate segmentally or supraspinally; further modulation results from processes initated by glial cells [5]. The neurochemistry of these processes involves an extraordinary array of compounds, including endorphins, neurokinins, prostaglandins, biogenic amines, GABA, neurotensin, cannabinoids, purines, and many others. Nociceptive pain may

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involve acute or chronic inflammation. The physiology of inflammation is complex. In addition to an immune component, retrograde release of substances from C polymodal nociceptors also may be involved. This "neurogenic inflammation" involves the release from nerve endings of compounds such as substance P, serotonin, histamine, acetylcholine, and bradykinin. These substances activate and sensitize other nociceptors. Prostaglandins produced by injured tissues also may enhance the nociceptive response to inflammation by lowering the threshold to noxious stimulation [6].

Neuropathic Pain and Its Mechanisms

Neuropathic pain is the pain syndrome inferred to result from direct injury or dysfunction of the peripheral or central nervous system. These changes may be caused by injury to either neural or non-neural tissues. There is an assumption that the fundamental mechanisms sustaining the pain have become independent of any ongoing tissue injury [7]. Neuropathic pain has varied characteristics. It may also be described as "dysesthetic" an uncomfortable, unfamiliar sensation such as burning, shock-like or tingling. Neuropathic pain syndromes may be associated with referred pain, allodynia (pain induced by non-noxious stimuli, *e.g.* light touch), hyperalgesia (increased response to a noxious stimuli), or hyperpathia (exaggerated pain responses following a stimulus, often with after-sensation and intense emotional reaction). Neuropathic pain syndrome is based on additional inferences of the primary location of the sustaining mechanisms [8].

Some of the neurophysiologic and neuroanatomic changes that may occur in peripherally-generated neuropathic pain are understood [9]. Injury to a peripheral nerve axon can result in abnormal nerve morphology. The damaged axon may grow multiple nerve sprouts, some of which form neuromas. These nerve sprouts, including those forming neuromas, can generate spontaneous activity, which peaks in intensity several weeks after injury. These areas of increased sensitivity are associated with a change in sodium receptor concentration, and other molecular processes, and also can occur at sites of demyelination or nerve fiber injury not associated with the severing of axons. Unlike normal nerve, these injured regions are more sensitive to physical stimuli, which is clinically associated with tenderness and the appearance of Tinel's sign (*i.e.*, pain or tingling when the area over a nerve is tapped). Some of these alterations in morphology and function result in peripheral sensitization, which may be related to a lower threshold for signaling or an expansion in receptive fields [11].

Psychological and "Idiopathic" Pain Mechanisms

There is an extremely complex relationship between the psyche and pain perception [12]. In some patients, the experience of persistent pain appears to induce disturbances in mood (reactive depression or anxiety) and other processes appear to worsen pain and pain-related distress. Other patients have premorbid or comorbid psychosocial concerns or psychiatric disorders that are best understood as evolving in parallel to the pain. These disturbances also can contribute to the pain experience and driver pain-related distress. Patients with personality disorders, substance use disorders, or mood disorders often are best served by primary treatment for the psychiatric problem at the same time that pain-related interventions are offered. On occasion, the psychological evaluation yields evidence that the pain itself is predominantly sustained by psychological factors. This phenomenon is known generically as "psychogenic" pain and is subject to the specific diagnoses codified under the Somatoform Disorders in the Diagnostic and Statistical Manual of the American Psychiatric Association [9]. The evidence for a somatoform disorder must be more than the mere lack of an identifiable physical etiology for the pain. It is very important that patients who have acute or persistent pain without a known physical source not be inappropriately labelled. This may lead to inadequate assessment in the future and therapeutic decisions that are inappropriately skewed; unfortunately, in many quarters, it also leads to stigmatization of the patient and the potential for greater suffering on this basis. When reasonable inferences about the sustaining pathophysiology of a pain syndrome cannot be made, and there is no positive evidence that the etiology is psychiatric, it is best to label the pain as "idiopathic" [6].

NOCICEPTORS

Receptors which respond primarily to injurious or painful stimulation are called nociceptors. Within this general category are four subgroups: a) mechano-nociceptors, b) mechano-heat nociceptors, c) mechano-cold nociceptors, and d) Polymodal nociceptors.

Distribution of the Nociceptors

Skin: Each of the four subgroups of nociceptors is represented in cutaneous tissue. While their terminal morphology is unknown, they are distinguished by their response patterns. Cutaneous mechanonociceptors are associated with type A delta fibers and respond to high shearing force. Cutaneous mechano-heat nociceptors respond to noxious levels of mechanical stimulation and heat in excess of 43°C. They are associated with certain myelinated type A delta fibers. On the other hand, cutaneous mechano-cold nociceptors are the terminal endings of certain non-myelinated type C fibers. They are particularly proficient at responding to noxious levels of mechanical stimulation and temperatures below 10°C. Polymodal nociceptors respond to noxious levels of mechanical, heat, and chemical stimulation and represent the terminal endings of certain non-myelinated type C fibers [10].

Muscles, Joints, and Viscera: Two types of muscle nociceptors have been identified. Pressure nociceptors respond to strong pressure and excessive muscle stretch.

Their terminal morphology is unknown and they are associated with myelinated group III fibers. Group IV nociceptors respond to strong pressure, temperature extremes, and anoxia. Their receptive elements are associated with nonmyelinated group IV fibers. Joint nociceptors are the peripheral ends of certain type A delta fibers. They respond to joint overextension and their terminal structures are unidentified. Pain receptors in the viscera are probably not located in the parenchyma of the internal organs themselves, but are found instead in the peritoneal surfaces, pleural membranes, dura mater, and the walls of blood vessels [10].

Pharmacology of Nociceptors

A nociceptive stimulus unleashes a cascade of events throughout the nervous system, which can ultimately lead (loop) back to the site of injury [13]. This response prompts cells of a variety of types in the injured area to release chemicals that trigger an immune response and influence the intensity and duration of pain [14].

On the basis of various reports, the following receptor types have been identified:

1. Opioid receptors
2. Cannabinoid receptors
3. Capsaicin and Vanilloid receptors
4. N-Methyl-D-Aspartate (NMDA) receptors
5. Purinergic receptors (ATP)
6. Miscellaneous receptor types

1. OPIOID RECEPTORS

Opioid receptors are a group of G-protein coupled receptors with opioids as ligands [15,16,17]. Opioid receptors possess the same general structure of an extracellular N-terminal region, seven transmembrane domains and intracellular C-terminal tail structure.

There are mainly three receptor types of opioid receptors that have been cloned, mu (μ), kappa (k) and delta (δ) [18]. A fourth receptor NOP (nociceptin opioid receptor), with high sequence homology to these three opioid receptors has also been identified. The NOP receptor is also involved along with other receptors in causing opioid reward and reinforcement. Types and distribution of these have been shown in Table 1.

Table 1. Major Subtypes of Opioid Receptors

Receptor	Subtypes	Location
delta (δ)	δ_1, δ_2	Brain (pontine nuclei, amygdala, olfactory bulbs, deep cortex Peripheral sensory neurons)
kappa (κ)	κ_1, κ_2, κ_3	Brain (hypothalamus, periaqueductal gray, claustrum Spinal cord (substantia gelatinosa) Peripheral sensory neurons
mu (μ)	μ_1, μ_2, μ_3	Brain [cortex (laminae III and IV), thalamus, striosomes, periaqueductal gray, rostral ventromedial medulla] Spinal cord (substantia gelatinosa) Peripheral sensory neurons Intestinal tract
Nociceptin opioid receptor (NOP)	ORL_1	Brain (cortex, amygdala, hippocampus, septal nuclei, habenula, hypothalamus) Spinal cord

In addition to the μ-, δ-, κ- and NOP-receptors, several other types of opioid receptor have been postulated. Since the contractions of the isolated vas deferens of the rat are much more sensitive to inhibition by β-endorphin than by other opioid peptides, it was suggested that this tissue contains a novel type of opioid receptor, the ε-receptor, which is specific for β- endorphin. The rabbit ileum has been proposed to possess ι-receptors, for which the enkephalins have high affinity but which are distinct from δ-receptors [19,20,21]. A very labile λ-binding site with high affinity for 4,5- epoxymorphinans has been found in freshly-prepared rat membrane fragments and there is evidence that opioids inhibit growth in S20Y murine blastoma cells by an action at yet another receptor type called the ζ- receptor. The ε-, λ-, ι- and ζ-receptors are poorly characterized and wider acceptance of their existence awaits further experimental evidence [21,25]. Although originally classified as such, the σ-receptor appears not to be an opioid receptor but rather the target for another class of abused drugs, phencyclidine (PCP) and its analogues. Phencyclidine is an effective blocker of the ion channel associated with the N-methyl-D-aspartate (NMDA) receptors [25,26].

Opioid Receptor Transducer Mechanisms

At molecular level all opioid receptors (including NOP receptor) are linked to G-protein. Actions commonly produced at these opioid receptors include [24]:

a) Inhibition of adenylate cyclase: Adenylate cyclase is an enzyme that breaks down adenosine triphosphate (ATP) to form cyclic adenosine monophosphate (cAMP). All three of opioid receptors couple to adenylate cyclase. Inhibition of adenylyl cyclase leads to decrease in intracellular cAMP with consequent decrease in cell excitability (mainly through μ and δ-receptors) [22,23].

b) Increased outward movement of K^+:

Many types of K^+ channels are now known, some of which are voltage-sensitive and others which are sensitive to intracellular substances. Opioid receptors open voltage-sensitive K^+ channels and thus increase outward movement of K^+ from neurons. This effect occurs in several brain regions as well as in the spinal cord and myenteric plexus. Increased outward movement of K^+ is the most likely mechanism for the postsynaptic hyperpolarisation and inhibition of neurons induced by opioids throughout the nervous system [22]. Activation of potassium channels and subsequent increase in K^+ conductance to produce hyperpolarisation of neurons and a decrease in their excitability due to increased outward movement of K^+ ions (mainly through μ and δ-receptors) [24].

c) *Decreased Ca^{2+} entry*:

Voltage-sensitive channels are activated only when there is depolarisation of the neuron. Three types of voltage-sensitive Ca^{2+} channels are known, the L-type (large conductance) sensitive to calcium channel blockers, the T-type (small conductance) and the N-type (intermediate conductance). Opioids inhibit N-type Ca^{2+} channels and thus inhibit neurotransmitter release [22]. This effect alone does not account fully for the effect of opioids on neurotransmitter release. However, inhibition of Ca^{2+} conductance by suppressing voltage gated N-type Ca^{2+} channel is mainly done through *k*-receptor [23].

Opioid agonists [25,26]: These are

(a) Morphine analogues:

Agonists- morphine, diamorphine (heroin), codeine, levorphanol

Partial agonists- nalorphine, levallorphan

(b) Synthetic derivatives unrelated to morphine:

Agonists - pethidine (meperidine), fentanyl, sufentanil, methadone, etorphine, dextro-propoxyphene

Partial agonists- pentazocine, cyclazocine, buperinorphine

Opioid Antagonists [25,26]: These are naloxone, naltrexone, nalmefene are pure opioid competitive antagonists of μ, k and δ receptors. The selective opioid receptor antagonist for μ, k and δ receptors are cyprodime, norbinaltorphmine and naltrindole, respectively.

2. CANNABINOID RECEPTORS

It is a class of cell membrane receptors under the G protein-coupled receptor superfamily [27]. The cannabinoid receptors contain seven transmembrane spanning domains. Cannabinoid receptors are activated by three major group of ligands, endocannabinoids (produced by the mammalian body), plant cannabinoids (such as Tetrahydrocannabinol (THC), produced by the cannabis plant) and synthetic cannabinoids (such as HU-210). All of the endocannabinoids and plant cannabinoids are lipophilic [28,29]. There are currently two known subtypes:-

CB_1: In 1992, the first cannabinoid receptor, CB_1 was cloned and classified as a member of the family of G protein-coupled receptors. The CB_1 cannabinoid receptor is found in high abundance in brain neurons, with highest levels expressed in basal ganglia, cerebellum, hippocampus and cerebral cortex [30]. Considerably lower expression is found in peripheral tissue including lung, testis, uterus, and vascular tissue. Following agonist binding, CB_1 receptors couple to the inhibition of adenylyl cyclase, inhibition of N- and Q-type voltage-operated calcium channels, and stimulation of inwardly rectifying and A type potassium channels.

CB_2: A second cannabinoid receptor, CB_2, was cloned in 1993 with 44% identity at the amino acid level to the CB_1 receptor. The CB_2 receptor is found in cells of the peripheral immune system and is coupled to inhibition of adenylyl cyclase, but does not appear to couple to ion channel regulation. CB_2 receptors are mainly expressed on T cells of the immune system, on macrophages and B cells, and in hematopoietic cells. They also have a function in keratinocytes, and are expressed on mouse pre-implantation embryos. It is also expressed on peripheral nerve terminals [31]. Recent research suggests that these receptors play a role in nociception, or the perception of pain. In the brain, they are mainly expressed by microglial cells, where their role remains unclear [32].

Receptor Distribution

CB_1 receptors are widely distributed but are particularly abundant in some areas of the brain including those concerned with movement and postural control, pain and sensory perception, memory, cognition, emotion, autonomic and endocrine functions [33]. They are also found in appetite regulating areas such as the hypothalamus as well as reward centres such as the lymbic system and have therefore been implicated in food intake. More recently, CB_1 has been isolated in tissues that are important for energy metabolism such as the liver, adipose tissue and skeletal muscle [34].

The second type of receptor, the CB_2 receptor, can mediate regulation of cytokine release from immune cells and of immune cell migration in a manner that seems to reduce inflammation and certain kinds of pain. So although the endocannabinoid system interacts with many neurotransmitter/neuromodulator systems it is important to note that phytocannabinoids have the ability to interact with all sorts of cellular pathways implicated in a range of diseases such as cancer and metabolic syndrome [35].

Mechanism of Action

Cannabinoids act as ligands (a small molecule able to dock onto the binding site of a protein) conferring their ability to modulate a receptor's behaviour and consequently their downstream biological pathways. Although the phytocannabinoids all have similar structures, they display a remarkably wide array of actions at each of the different receptors that are now thought to contribute to the endocannabinoid system (such as cannabinoid receptors,

transient receptor potential [TRP] channels, melatonin and serotonin receptors, the PPARs and a host of orphan G-coupled receptors) [34]. For example it is known that THC positively regulates the CB1 receptor whereas it is negatively regulated by Tetrahydrocannabivarin (THCV); interestingly CBD has very little action at this site whatsoever [35].

Endocannabinoids act as partial agonists, playing modulatory roles, and because phytocannabinoids behave in a similar fashion they can offer help within a dysregulated endocannabinoid system.

CB_1 receptors are coupled through $G_{i/o}$ proteins and inhibit adenylyl cyclase and activate mitogen-activated protein (MAP) kinase. In addition, CB_1 receptors inhibit presynaptic N- and P/Q-type calcium channels and activate inwardly rectifying potassium channels [31,36]. CB_1 receptors are highly expressed in hypothalamic areas which are involved in central food intake control and feeding behaviour. This strongly indicates that the cannabinoid system is directly involved in feeding regulation. These regions are also interconnected with the mesolimbic dopamine pathway, the so-called "reward" system [32]. Therefore, CB_1 antagonists might indirectly inhibit the dopamine-mediated rewarding properties of food. Peripheral CB_1 receptors are located in the gastrointestinal (GI) tract, liver and in adipose tissue. In the GI, CB_1 receptors are located on nerve terminals in the intestines. Endocannabinoids act at the CB_1 receptors to increase hunger and promote feeding and it is speculated that they decrease intestinal peristalsis and gastric emptying [37]. Thus, antagonism at these receptors can inverse these effects. Also, in peripheral tissues, antagonism of CB_1 receptors increases insulin sensitivity and oxidation of fatty acids in muscles and the liver [38].

CB1 Agonists: Endogenous Agonists: Anandamide (A 0580), 2-Arachidonyl glycerol (A-261) [39,40]; Receptor selective Agonists: Δ9-THC (T 2386), CP-55,940 (C 1112), R(+)-WIN 55,212-2 (W-102), HU 210 (H 7909), levonantradol, nabilone, methanandamide (M-186), JWH-015 (J 4252) [41,42]

CB_1 Receptor Antagonist: SR 141716A or Rimonabant (CB_1 antagonist) and SR 144528 (CB_2 antagonist) [29,43]

Rimonabant, also known by the systematic name [N-(piperidin-1-yl) -5- (4-chlorophenyl) -1- (2,4-dichlorophenyl) -4 -methyl -1 H-pyrazole-3-carboxamide-hydrochloride)], is a 1,5-diarylpyrazole CB_1 receptor antagonist. Rimonabant is not only a potent and highly selective ligand of the CB_1 receptor, but it is also orally active and antagonizes most of the effects of cannabinoid agonists, such as THC, both *in vitro* and *in vivo*. Rimonabant has been reported in many cases to behave as an inverse agonist rather than as a neutral antagonist and it is likely that it binds preferentially to the inactive state of the CB_1, thereby decreasing the activation of the signaling pathway [44,45]. Rimonabant analogs have recently been described by several groups which has led to a good understanding of the structure-activity relationship (SAR) within this chemical group. While most analogs are less potent than SR141716, two of them are worth mentioning, SR147778 and AM251 [46]. SR147778 (Surinabant), a second generation antagonist, has a longer duration of action than rimonabant and enhanced oral activity. This enhanced duration of action is probably due to the presence of the more metabolically stable ethyl group at the 4-position of its pyrazole ring. Another change is the replacement of the 5-phenyl chlorine substituent by bromine [47,48]. The diarylpyrazole derivative, AM251, has been described where chlorine substituent has been replaced by iodine in the *para* position of the 5-phenyl ring. This derivative appeared to be more potent and selective than rimonabant [49,50].

3. CAPSAICIN RECEPTORS

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) the pungent ingredient of hot chilli peppers that gives them their burning sensation or piquancy was first isolated in the nineteenth century. Interest in the sensory effects of capsaicin has a very long history. The effects of capsaicin are best understood in terms of its excitatory and desensitizing actions on polymodal nociceptors. Electrophysiological studies reveal that capsaicin depolarizes Diagnosis-related group (DRG) neurons and decreases their input resistance in a concentration dependent manner, suggesting that the specific excitatory effect of capsaicin on nociceptive neurons involves an increase in membrane permeability to ions such as sodium and/or calcium.

(i) Vanilloid Receptor (TRPV1)

The vanilloid receptor (TRPV1) is one of the six sub-members that belong to the transient receptor potential channel (TRP) superfamily. TRPV1 was the first mammalian member to be discovered and is a non-selective cation channel permeable for calcium. The receptor is made of four identical subunits each with six transmembrane segments S1-S6, with an aqueous pore situated between fifth and sixth segment. This region forms the channel conductive pore and contains the N- and C-termini on the cytosolic side of the cell membrane [51]. Besides being activated by capsaicin, TRPV1 also responds to a wide range of exogenous and endogenous chemical ligands as well as physical stimuli such as heat over 42°C and changes in more diverse activators such as protons (acid, pH<6). TRPV1 is also subject to regulation by changes in membrane potential and this intrinsic voltage-dependence is thought to underlie the gating mechanism of this non-selective cation channel which leads to the influx of sodium and calcium ions. Importantly, TRPV1 activity is also subject to regulation by a host of intracellular signalling cascades such as G-protein coupled receptor signalling, that are implicated in the responses to algogenic agents, inflammatory mediators and injury [52].

Mechanism of action: TRPV1 is primarily expressed on small myelinated and unmyelinated medium size sensory neurons in dorsal root and trigeminal ganglia, where sensory neurons cluster. TRPV1 receptors are also found in muscles, joints, the urinary bladder and kidneys [53]. The functional activity of TRPV1 has been demonstrated within the central nervous system, in the spinal cord and in specific sites in the brain including the hypothalamus, cerebellum, locus coeruleus, periaqueductal grey and cortex. Activation of TRPV1 sets off an influx of calcium and sodium ions which in turn initiates a cascade of events that result in membrane depolarisation, neuronal firing and transduction of neural impulses [54]. TRPV1 phosphorylates as a response to several algesic agents, resulting in a lower threshold of channel activation. Some substances such as bradykinin, nerve growth factor and protons have been reported to sensitize the TRPV1 receptor. Activation of TRPV1 results in the release of pro-nociceptive peptides, which decreases when treated with TRPV1 antagonists. In general, most channel antagonists bind in the pore region, interacting with residues from all four monomers of the tetrameric channel [55].

Agonists: Agonists such as capsaicin and resinifertoxin activate TRPV1, and upon prolonged application, TRPV1 activity would decrease (desensitization), leading to alleviation of pain.

Antagonists: Experiments have shown that TRPV1 blockade increases body temperature in multiple species, including rodents and humans, suggesting that TRPV1 is involved in body temperature maintenance [56]. Recently, AMG 517, a highly selective TRPV1 antagonist was dropped out of clinical trials due to the undesirable level of hyperthermia [57]. A second molecule, SB-705498 was also evaluated in the clinic but its effect on body temperature was not reported [58]. Recently, it was disclosed that clinical trials of two more TRPV1 antagonists, GRC 6211 and NGD 8243 have been stopped.

(ii) TRPV2

TRPV2 is closely related to the capsaicin receptor TRPV1, with which it shares 49% sequence identity, however TRPV1 is activated by capsaicin and responds to temperatures above 43°C whereas TRPV2 does not respond to capsaicin and responds to temperatures at or above 52°C. TRPV2 is expressed in a variety of tissues including various regions of the brain, spinal cord and sensory ganglia. Its expression in tissues that are never exposed to temperatures as high as 52°C suggests that TRPV2 is normally activated by stimuli other than noxious heat in these regions of the body.

Activators and inhibitors: TRPV2 is activated by high temperatures above 52°C. Alternatively it can be activated at lower temperatures by chemicals, such as the research tool 2-Aminoethoxydiphenyl borate (2-APB) [59], the plant cannabinoid, cannabidiol [60] and probenecid [61]. It is blocked by ruthenium red and lanthanum [62].

(iii) TRPV3

The TRPV3 protein belongs to a family of nonselective cation channels that function in a variety of processes, including temperature sensation and vasoregulation. The thermo-sensitive members of this family are expressed in subsets of sensory neurons that terminate in the skin, and are activated at distinct physiological temperatures. This channel is activated at temperatures between 22°C and 40°C. The gene lies in close proximity to another family member (TRPV1) gene on chromosome 17, and the two encoded proteins are thought to associate with each other to form heteromeric channels [62]. TRPV3 is closely related to TRPV1 and TRPV2 with which it shares 43% and 41% sequence identity respectively. TRPV3 has a unique threshold: It is activated at innocuous temperatures with an activation threshold around 33°C to 35°C and exhibits increasing responses at higher noxious temperatures. As reported for TRPV1 knockout mice TRPV3 knockout mice exhibited behavioural deficits in their response to hot temperatures at or above 50°C. TRPV3 and TRPV1 thus seem to have overlapping functions in noxious heat sensation.

(iv) TRPV4

TRPV4 is a calcium permeable nonselective cation channel that shares 40% amino acid identity with TRPV1. It exhibits remarkable gating properties being activated by hypotonic solutions, by certain phorbol ester derivatives and by innocuous temperatures in the range of 27°C to 34°C. Activation by hypotonic solutions suggests that it serves as a sensor for osmolarity and/or mechanical stretch associated with cellular swelling. Additionally TRPV4 is activated by a process involving the cytochrome P450 epoxygenase dependent formation of epoxyeicosatrienoic acids: submicromolar concentrations of 5',6' - epoxyeicosatrienoic acid activates TRPV4. These findings indicate that TRPV4 can be activated by a range of physical and chemical stimuli which may or may not share a common mechanism. TRPV4 appears to play a role in thermal hyperalgesia: TRPV4 knockout mice exhibited a reduced hyperalgesia from 35–45°C but not at 50°C [63]. This study failed to find alterations in acute thermal behavior in TRPV4 knockout mice whereas another study [64] found longer withdrawal latencies during acute tail heating at 45°C –46°C, suggesting a role for TRPV4 in acute heat nociception. In summary, of the TRPV channels studied with genetic knockout studies (TRPV1, TRPV3, and TRPV4) TRPV1 and TRPV3 have been shown to play a role in thermal nociception.

(v) TRPA1

TRPA1 ion channels are activated by irritant compounds from mustard seed, wasabi, horseradish, winter green, cinnamon, garlic, vehicle exhaust fumes and tear

gas, all of which elicit a painful burning or pricking sensation. TRPA1 is expressed in DRG neurons and in the inner ear; however, TRPA1 is apparently not essential for the initial detection of sound by hair cells. The role of TRPA1 as a sensor of noxious cold has been controversial; mouse TRPA1 when expressed in CHO cells is activated at temperatures starting near 17°C, which is close to the threshold of noxious cold for humans (15°C) [65]. The controversy arose when the rat and human orthologues of TRPA1 expressed in either a human embryonic kidney (HEK293) cell-line or *Xenopus* oocytes were not activated by cold [66]. Subsequently, another group was unable to elicit cold activation of heterologously expressed mouse TRPA1 channels in HEK293 cells [67]. Yet a fourth study [68] found that mouse TRPA1 expressed in HEK293 cells is a cold-activated channel, which supports the previous findings that TRPA1 responds to noxious cold. The controversy also extended to TRPA1 knockout mice. Nociceptive behavioural responses to contact with a cold surface or to acetone evoked evaporative cooling were evaluated by two different groups [69,70] with one finding a lack of involvement of TRPA1 in the acute detection of cold and the other finding a reduced sensitivity to cooling. These contradictory findings regarding the cold activation of TRPA1 appear to have been resolved by subsequent work. A study in mice in which all sensory neurons expressing the tetrodotoxin resistant voltage activated sodium channel were eliminated, showed resistance to noxious cold, assayed using a cold plate at 0°C [71]. This finding was similar to what was observed in the TRPA1 knockout mice using a cold plate at 0°C [70]. Significantly, the NaV1.8 knockout mice also exhibited a significant reduction in the expression of TRPA1 in DRG neurons and a lack a TRPA1-mediated nociceptive response to formalin. Thus, TRPA1 appears to be the sensor for noxious cold at 0°C. Furthermore, a later study provided a plausible explanation for the discrepancies in the earlier work described above [72]. In contrast to the debate over the role of TRPA1 as a sensor of noxious cold its role in bradykinin evoked nociceptor excitation and pain hypersensitivity was not controversial. Bradykinin (BK) is a peptide containing nine amino acid residues (nona-peptide) that is released into inflamed tissues where it induces pain and mechanical and thermal hypersensitivity. Bradykinin injections in TRPA1 knockout mice were much less painful and showed little or no evidence of thermal or mechanical hypersensitivity following the injections. Both consequences are expected if TRPA1 mediates the actions of bradykinin.

(vi) TRPM8

The ability of recombinant TRPM8 to be activated by cold is widely accepted. TRPM8 is activated by cooling agents such as menthol or at temperatures below 26°C. Additionally, three independent studies using TRPM8 knockout mice [73,74,75] indicate that TRPM8 is involved in sensing noxious cold. Pain-induced by evaporative cooling of the paw was measured by observing licking and flinching responses of the stimulated paw in normal and TRPM8 knockout mice: the knockout mice displayed significantly reduced behaviour compared to the normal mice [73]. A similar result was found by others [75] who additionally found that "… injection of icilin, a synthetic compound that activates TRPM8 and, to a much lesser extent, TRPA1, into the hind paw of wild-type mice causes the rapid induction of hind paw withdrawal when the mice are placed on a 1°C cold plate and that this behaviour is completely ablated in TRPM8 knockout mice, suggesting that TRPM8 activation can elicit a nociceptive-like response." The third group [74] also found a reduced nociceptive response to evaporative cooling of the paw in TRPM8 knockout mice. Furthermore, these authors also found that following constriction injury caused by ligation of the sciatic nerve normal mice exhibited an enhanced sensitivity to acetone with protracted licking and shaking of the paw whereas TRPM8 knockout mice exhibited no significant increase in the response to evaporative cooling of the paw. These data indicate that TRPM8 is involved in sensing noxious cold. TRPM8 knockout mice retain a number of cold sensitive neurons indicating that TRPM8 is not the only receptor activated by cold. Combined knockouts of TRPA1 and TRPM8 might help clarify the relative role of TRPA1 and TRPM8 in the detection of noxious cold.

4. NMDA RECEPTORS

The NMDA receptor (NMDAR), a glutamate receptor, is the predominant molecular device for controlling synaptic plasticity and memory function. The NMDAR is a specific type of ionotropic glutamate receptor. A major advance in this field came in the late 1980s when two groups demonstrated that the spinal delivery of N-methyl-d-aspartate (NMDA) receptor (NMDAR) antagonists inhibits the hyperexcitability of spinal cord nociceptive neurons induced by C-fiber stimulation [76,77]. NMDA (N-Methyl-D-Aspartate) is the name of a selective agonist that binds to NMDA receptors but not to other glutamate receptors. Glutamate, the major excitatory neurotransmitter in the brain and spinal cord, exerts its postsynaptic effects via a diverse set of membrane receptors, ionotropic, and metabotropic. Ionotropic receptors directly gate ion channels and are divided into three major subclasses: AMPA (2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid), kainate, and NMDA, named according to the types of synthetic agonists that activate them (α-amino- 3-hydroxy-5-methyl-4-isoxasolepropionic acid, kainate, and N-methyl-d-aspartate, respectively). Of these, NMDARs have received particular attention because of their crucial roles in excitatory synaptic transmission, plasticity, and neurodegeneration in the central nervous system (CNS). Activation of NMDA receptors results in the opening of an ion channel that is nonselective to cations with an equilibrium potential near 0 mV. A unique property of the NMDA receptor is its voltage-dependent activation, a result of ion channel block

by extracellular Mg^{2+} ions. This allows the flow of Na^{+} and small amounts of Ca^{2+} ions into the cell and K^{+} out of the cell to be voltage-dependent [78,79,80,81]. Calcium flux through NMDARs is thought be critical in synaptic plasticity, a cellular mechanism for learning and memory. The NMDA receptor is distinct in two ways: first, it is both ligand-gated and voltage-dependent; second, it requires co-activation by two ligands: glutamate and glycine. NMDARs are composed of NR1, NR2 and NR3 subunits. Co-expression studies have demonstrated that formation of functional NMDAR channels requires a combination of NR1, an essential channel-forming subunit, and at least one of the NR2 subunits [82]. Site-directed mutagenesis and molecular modeling studies have disclosed critical determinants of the glutamate and glycine binding sites and demonstrated that they are located on the homologous regions of the NR2 and NR1 subunits, respectively [83]. The co-expression studies have also shown that many biophysical and pharmacological properties of the heteromeric NR1/NR2 NMDAR channels, such as sensitivity to magnesium block, kinetics of desensitization and offset decay, susceptibility to modulation by glycine, reducing agents, polyamines and phosphorylation, and affinity for agonists and antagonists, depend on the type of NR2 subunit included in a heteromeric complex [80,84]. There is considerable evidence that pain associated with peripheral tissue or nerve injury involves NMDAR activation. NMDAR antagonists have been shown to effectively alleviate pain related behaviour in animal models as well as in clinical situations [85,86]. However, NMDARs are important for normal CNS functions, and the use of NMDAR antagonists can often be limited by serious side effects, such as memory impairment, psychotomimetic effects, ataxia, and motor in co-ordination.

Agonists: Aminocyclopropanecarboxylic acid, D-Cycloserine, Cis-2,3-Piperidinecarboxylic acid, L-aspartate, Quinolinate, Homocysterate, D-serine, L-alanine.
Antagonists: Amantadine, Ketamine, Phencyclidine, Nitrous oxide, Dextromethorphan and dextrophan, Memantine, Ethanol, Riluzole (used in ALS), Xenon, HU-211 (also a cannabinoid), Lead (Pb^{2+}), Conantokins, Huperzine A.

Dual opioids and NMDA-Antagonists: Ketobemidone, Methadone, Dextropropoxyphene, Tramadol, Kratom alkaloids and Ibogaine [87]

5. PURINERGIC RECEPTORS

The term purinergic receptor (or purinoceptor) was first introduced to describe classes of membrane receptors that, when activated by either neurally released ATP (P2 purinoceptor) or its breakdown product adenosine (P1 purinoceptor), mediated relaxation of gut smooth muscle [88,89]. According to pharmacological profile and tissue distribution [,90,91,92,93] P2 purinoceptors were further divided into five broad phenotypes (P2X, P2Y, P2Z, P2U, and P2T). Thereafter, they were reorganized into families of metabotropic ATP receptors (P2Y, P2U, and P2T) and ionotropic ATP receptors (P2X and P2Z) [94], later redefined as extended P2Y and P2X families [95]. In the early 1990s, cDNAs were isolated for three hepta-helical proteins-called P2Y1, P2Y2, and P2Y3-with structural similarities to the rhodopsin GPCR template. At first, these three GPCRs were believed to correspond to the P2Y, P2U, and P2T receptors. However, the complexity of the P2Y receptor family was underestimated. At least 15, possibly 16, heptahelical proteins have been associated with the P2Y receptor family [96]. Multiple expressions of P2Y receptors is considered the norm in all tissues [97] and mixtures of P2 purinoceptors have been reported in central neurones [98] and glia [99]. The situation is compounded by P2Y protein dimerization to generate receptor assemblies with subtly distinct pharmacological properties from their constituent components [100]. Also, the range of naturally occurring nucleotides capable of stimulating P2Y receptors has extended beyond ATP and its immediate breakdown products [101].

Signal transduction and receptor modulation

Most of the recombinant P2Y receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11) couple via the Gq/PLCβ pathway to cause IP_3 production, Ca^{2+}-mobilization and activation of Ca^{2+} dependent reporter currents in heterologous expression systems [96]. When expressed in cultured sympathetic neurones, some P2Y receptors inhibit native Ca^{2+} and K^{+} currents by a direct action on ion channels by G protein catalytic and regulatory subunits [100]. Endogenous metabotropic P2 receptors affect a much wider range of intracellular signalling pathways and utilize PLCβ, PLD, PLA2, AC, MEP/MAP kinases and Rho-dependent kinase, as well as coupling directly to some ion channels. The narrow selectivity of recombinant P2Y subtypes may only reflect the limited availability of signalling pathways in expression systems used so far. A native P2Y1-like receptor, in the clonal line (B10) of rat brain capillary endothelial cells, appeared to couple negatively to adenylate cyclase and inhibit cAMP levels through a PTX-sensitive G protein [102]. The possibility that recombinant rP2Y1 receptors might affect cAMP production was investigated by expression into 1321N1 and C6 rat glioma cells that, respectively, utilize Gq/PLCβ and Gi/AC signalling mechanisms [103]. Experiments showed that rat P2Y1 receptors selected only the Gq/PLCβ pathway in 1321N1 cells, and not the Gi/AC pathway in C6 glioma cells. Although B10 cells possess P2Y1 transcripts, it was later shown that B10 cells also possessed a P2Y12-like receptor that could activate the Gi/AC pathway and help explain earlier results [104]. The available evidence suggests that known species orthologues of P2Y1 couple primarily to the Gq/PLCβ pathway. The skate P2Y receptor, considered to be the most primitive form of P2Y1, is the only GPCR in skate liver to signal via the Gq/PLCβ pathway [105]. Apart from the Gq/PLCβ signalling, P2Y1

receptors directly inhibit N-type Ca^{2+}-currents in rat sympathetic neurones [100]. The P2Y2 receptor appears to couple mainly to the Gq/PLCβ pathway, although 35 percent of the evoked Ca^{2+}-signal is inhibited by PTX [101,102,106,107]. PLCβ activation, via Gα of PTX-insensitive Gq and Gβ,γ complex of PTX-sensitive Gi, could account for the P2Y2-induced Ca^{2+}-signal [108]. In *Xenopus* oocytes, P2Y2 receptors couple directly to co-expressed K^+ channels of the Kir3.0 subfamily via PTX-sensitive Gi/o proteins [109]. In sympathetic neurons, P2Y2 receptors inhibit N-type Ca^{2+}-currents via a PTX-sensitive mechanism [110,111]. A native P2Y2- like receptor, in canine MDCK-D1 epithelial cells, was reported to couple indirectly to Gs/AC through an indomethacin-sensitive pathway [112]. Dual signalling also occurs with the human P2Y4 receptor, since PTX limits the Ca^{2+} signal by 60 percent in the first 30s of agonist activation but fails to inhibit Ca^{2+} levels following prolonged (>300 s) agonist activation [113]. By contrast, P2Y6 receptor signalling via Ca^{2+} mobilisation was reported to be PTX-insensitive [114,115]. However, P2Y6 receptors inhibit N-type Ca^{2+}-currents via a PTX-sensitive mechanism in sympathetic neurons [116]. The P2Y11 receptor couples strongly to the Gq/PLCβ pathway, but also activates the Gs/AC pathway [117,118,119]. It was reported that inositol hydrolysis and Ca^{2+}-mobilisation, via the Gq/PLCβ pathway, could potentiate cAMP production via the Gs/AC pathway in 1321N1 and CHO-K1 cells [119]. This potentiating effect may help explain differences in agonist potencies when a range of nucleotides was tested against the two signalling pathways [117,119]. The signalling and pharmacological properties of P2Y11 mirror the endogenous P2Y receptor in HL-60 cells [120,122]. P2Y1 receptors couple to the Gi/AC pathway to inhibit AMP production, an effect blunted by PTX [122]. While human P2Y12 receptors directly inhibit cAMP production in CHO (Chinese Hamster Ovary) cells, receptor activation was otherwise assessed in oocytes by Gβ, γ subunit stimulation of ion channels co-expressed with P2Y12.

Agonists: Human P2Y1 receptors are activated fully by ADP and the naturally occurring dinucleotide, Ap4A. ATP can act either as a full agonist, partial agonist, or antagonist depending on receptor reserve. Other mononucleotides (e.g. CTP, GTP, ITP, UTP and their immediate breakdown products) are inactive. The synthetic alkylthio-ATP derivatives are potent agonists (e.g. 2-MeSATP, 2-MeSADP, 2-HT-ATP, PAPET-ATP), as are phosphorothioate ATP derivatives (e.g. ATPγS and ADPβS), while methylene phosphonate-ATP derivatives (α, β- meATP and β, γ-meATP) are inert [101]. At recombinant P2Y1 receptors, dATPαS is either a weak agonist [104] or an antagonist [96], whereas at P2Y1-like receptors in rat brain, ATPαS and ATP are equipotent agonists [122]. Human P2Y2 receptors are activated equally by ATP and UTP, as well as by the dinucleotides Ap4A and Up4U [123]. The phosphorothioate derivatives ATPγS and UTPγS are potent stimulants, but other major classes of synthetic nucleotides are not. Human P2Y4 receptors are activated by UTP and Up3U [123], while CTP, GTP, ITP, and Ap4A are considered to be weak agonists [101]. In contrast, rat and mouse P2Y4 receptors are activated equally by UTP and ATP. Human P2Y6 receptors are activated by UDP and, to a lesser extent, ADP with all other nucleoside triphosphates being very weak agonists [124]. Of the synthetic compounds, UDPβS and Up3U are both potent agonists at P2Y6 receptors [123,125]. Rats and mouse orthologues show a similar pharmacological profile to human P2Y6 [116,126]. The human P2Y11 receptor is activated by ATP and ADP [117] and the synthetic nucleotides BzATP, deoxyATP, 2-MeSATP, and AR-C67085 (2-propyl-d-β, γ-dichloromethylene-ATP) are also all potent agonists [117,119]. In contrast, some synthetic nucleotides, like ADPβS, ATPγS, and A3P5PS are partial agonists, although, under some circumstances, they can also act as antagonists [117]. Human P2Y12 receptors are activated by ADP, 2-MeSADP and to a lesser extent by ATPγS.

Antagonists: Some synthetic adenosine 3,5-bisphosphate derivatives are potent antagonists (e.g. MRS 2179 and MRS 2279) [127] at P2Y1 receptors and the classical P2 receptor antagonists (PPADS, Reactive blue-2 and suramin) also inhibit P2Y1 receptor activity. Suramin is also the one and only weak antagonist of P2Y2 receptors. For human P2Y4, ATP is reported to be the most potent competitive antagonist [128]. Weak antagonist activity has also been reported for PPADS, suramin and Reactive blue-2 at P2Y4, P2Y6, and P2Y11 receptors [115,126,129]. Human P2Y12 is antagonized by 2-MeSAMP and C13307 [130], while the native form of the receptor is potently blocked by ARC67085 [131]. P2Y1 antagonists, in the form of adenosine 3, 5-bisphosphate derivatives are inert at human P2Y12.

6. MISCELLANEOUS RECEPTORS:

(i) Proteinase-Activated Receptors:

Proteases in the circulation which are generated during tissue injury have been shown to activate a family of G-protein coupled, proteinase-activated receptors (PARs). These PARs play a role in hemostasis, inflammation, and pain. The proteases cleave extracellular N-terminal domains of the PARs to expose tethered ligands that bind to and activate the cleaved receptors. Four PARs have been identified by molecular cloning: PAR1, PAR2, PAR3 and PAR4. Of these, PAR1 and PAR2 are present on DRG neurons and have been shown to play a role in neurogenic inflammation, that is, inflammatory symptoms that result from the release of substances from primary sensory nerve terminals. PAR2 is activated by the serine proteases tryptase and trypsin [117]. Although trypsin is able to activate PAR2, trypsin itself is not present in most tissues, thus, it is probably not the endogenous enzyme that activates PAR2. Conversely, tryptase is released during

human mast cell degranulation and is able to cleave PAR2 in cells normally expressing PAR2 or in cells transfected with the receptor. Therefore tryptase is a likely candidate for the enzyme that activates PAR2. Thrombin appears to be the most likely agonist to activate neuronal PAR1 [117].

(ii) Endothelin Receptors:

The endogenous endothelin (ET) peptides participate in a remarkable variety of pain-related processes. ET_A receptors have been found on a large proportion of the cell bodies of small-diameter sensory neurons (DRGs), which are associated with C- and Aδ-fibers that carry pain impulses [132]. Moreover, activation of these nociceptive fibers by ET-1 is blocked by BQ-123, an ET_A receptor antagonist [133]. Together, these studies strongly argue for a selective role of peripheral ET_A receptors in the induction of pain through nociceptive fibers. The receptor pathways involved in pain generation by ET-1 are complex. ETA receptor activation sometimes elicits a rise in intracellular calcium [134,135], which is probably mediated by Gaq/11, acting through PLC to release Ca^{+2} from intracellular stores, and also through stimulation of guanylyl cyclase (GC). The latter enzyme converts GTP to cGMP, which can activate protein kinase G, affecting an anti-nociceptive response [136]. This pathway is complicated, however, since cGMP is also elevated by NO [137], a substance that has a positive role in mediating inflammatory hyperalgesia [138]. In addition, GTP itself enhances the activation of Na^+ current in small sensory neurons [139], in a PKC-dependent way [140], an effect that would be diminished by the nucleotide's conversion to cGMP. From this complex of information it is not possible to determine the overall change in sensory processing that result from elevation of cGMP by ET-1. In addition to elevating Ca^{2+} in peripheral sensory neurons, ET-1 stimulates (Ca^{2+}-independent) PKC-ε– mediated phosphorylation and concomitant functional enhancement of the TRPV1 channels present on nociceptive C-fibers [141].

Serotonin Receptors:

Descending serotoninergic facilitatory pathways are involved in neuropathic pain. These pathways may involve 5-HT2A receptors known to play a role in spinal and peripheral sensitization [142].

(iii) Prostaglandin Receptors:

Prostaglandin E2 (PGE2) is considered to be a key mediator in migraine pathophysiology. PGE2 acts via four receptors (EP1–EP4) but their distribution in the brain districts implicated in migraine has yet to be delineated [143].

CONCLUSION

Thus pain, though looks like a simple physiological term involves a complex interplay of various factors and receptors. Probably a more intensified research may reveal more important players in the near future; and as our understanding of pain receptors increases, it will help new drugs to be brought into the market.

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