Inhibitory Actions of Clinical Analgesics, Analgesic Adjuvants, and Plant-Derived Analgesics on Nerve Action Potential Conduction

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The action potential (AP) conduction in nerve fibers plays a crucial role in transmitting nociceptive information from the periphery to the cerebral cortex. Nerve AP conduction inhibition possibly results in analgesia. It is well-known that many analgesics suppress nerve AP conduction and voltage-dependent sodium and potassium channels that are involved in producing APs. The compound action potential (CAP) recorded from a bundle of nerve fibers is a guide for knowing if analgesics affect nerve AP conduction. This entry mentions the inhibitory effects of clinically used analgesics, analgesic adjuvants, and plant-derived analgesics on fast-conducting CAPs and voltage-dependent sodium and potassium channels. The efficacies of their effects were compared among the compounds, and it was revealed that some of the compounds have similar efficacies in suppressing CAPs. It is suggested that analgesics-induced nerve AP conduction inhibition may contribute to at least a part of their analgesic effects.

antinociception analgesic analgesic adjuvant plant-derived compound nerve conduction sciatic nerve compound action potential sodium channel potassium channel

Signal of painful stimuli applied to the skin is mainly conveyed by primary-afferent thin myelinated Aδ-fibers and unmyelinated C-fibers to the spinal cord and brain stem; the information is then transmitted to the brain by the conduction of action potentials (APs) in nerve fibers and chemical transmission at neuron-to-neuron junctions [1][2][3][4]. Acute nociceptive pain caused by tissue injury or damage is a physiological mechanism that serves to protect a person against injury, which is usually alleviated by antipyretic analgesics including non-steroidal anti-inflammatory drugs (NSAIDs) and narcotic analgesics such as opioids. On the other hand, chronic pain, which may last for a long time, such as three months or more, or occur repeatedly, is a debilitating disease accompanied by spontaneous pain, etc. and is often resistant to analgesics such as NSAIDs and opioids. Neuropathic pain, which is one type of chronic pain, results from a direct injury given to the peripheral nervous system (PNS) and damage caused in the central nervous system (CNS), and it is characterized by an excessive rise in the excitability of neurons in the vicinity of injured or damaged neuronal tissues [5]. This type of pain is alleviated by using analgesic adjuvants such as local anesthetics, antiepileptics, antidepressants, and α_2-adrenoceptor agonists [6][7][8][9][10][11][12][13][14][15]. Although analgesics and analgesic adjuvants generally depress excitatory synaptic transmission [16][17][18], many of their drugs can possibly suppress nerve AP conduction, which in part contributes to their inhibitory effects on pain. Plants and their constituents are used as folk remedies to relieve pain as a drug with few side effects [19][20][21].

AP conduction is produced by the activation of voltage-dependent sodium and potassium channels expressed in nerve fibers. Thus, a stimulus that induces membrane depolarization, applied to a certain point on a nerve fiber, opens a sodium channel, resulting in an influx of sodium ion into the cell according to the concentration and potential gradient across the cell membrane. This leads to AP production in a self-renewing manner, which in turn causes an outward current, i.e., membrane depolarization, to open other sodium channels at the points next to it. Such an AP production is subsided by subsequent sodium channel inactivation and potassium channel opening [22][23].

Isolation Methods for Testing Analgesic Action on Nerve Fibers

The study of AP in mammals is complicated by the need to dissect out individual nerves to isolate them from peripheral stimulation. For this reason, neuroscience relies on nerve extraction from relatively simple animals with conserved AP mechanisms, such as insects, reptiles, squids, or frogs (for example, refer to [23]).

AP current flowing on the surface of a nerve trunk consisting of many fibers can be measured as a compound action potential (CAP) by immersing the nerve in an isolator such as air, oil, or sucrose, and then by putting two electrodes on the nerve. CAPs, which are sensitive to tetrodotoxin (TTX), that blocks voltage-dependent sodium channels, and are fast-conducting (possibly mediated by primary-afferent thick myelinated Aα fibers), can be easily observed in the sciatic nerve trunk isolated from frogs by exposing the nerve trunk to air (known as the air-gap method). A half-peak duration of the CAP was increased by a voltage-dependent delayed rectifier potassium channel inhibitor, tetraethylammonium, without any alteration in its peak amplitude, which indicated that potassium channels are involved in CAP production [24]. Although the frog sciatic nerve exhibits both fast-conducting and slow-conducting (Aδ-fiber and C-fiber mediated) CAPs, the latter CAPs have much smaller peak amplitudes and conduction velocities than the former ones [25].

Fast-conducting CAPs recorded from the frog sciatic nerve were found to be inhibited by antinociceptive drugs in a manner dependent on their concentrations and chemical structures. Among the drugs, there are clinically used antinociceptive drugs including NSAIDs [26], many types of opioids such as tramadol [27][28], many amide- and ester-type local anesthetics [29], antiepileptics [30], antidepressants [31], dexmedetomidine (DEX; (+)-(*S*)-4-[1-(2,3-dimethylphenyl)-ethyl]-1H-imidazole, which is an α_2-adrenoceptor agonist; [32]), and diverse kinds of antinociceptive compounds isolated from plants [33]. This entry will describe the effects of antinociceptive drugs on CAPs evoked in the sciatic nerves of frogs and argue how nerve AP conduction inhibitions produced by drugs differ among them. For comparison, the effects of antinociceptive drugs on peripheral nerve CAPs in mammals and voltage-dependent sodium and potassium channels that are involved in producing APs will also be mentioned, provided that data are available.

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