The pharmacological basis of opioids

Carla Ghelardini[1]
Lorenzo Di Cesare Mannelli[1]
Enrica Bianchi[2]

[1] Department of Neuroscience, Psychology, Drug Research and Child Health - NEUROFARBA - Pharmacology and Toxicology Section, University of Florence, Florence, Italy
[2] Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

Address for correspondence:
Carla Ghelardini
Department of Neuroscience, Psychology, Drug Research and Child Health - NEUROFARBA - Pharmacology and Toxicology Section, University of Florence
Viale Pieraccini 6, 50139, Florence, Italy
E-mail: carla.ghelardini@unifi.it

Summary

An opioid is a chemical that binds to opioid receptors, which are widely distributed in the central and peripheral nervous system and gastrointestinal tract. The different effects elicited by activation of these receptors are due to their specific neuronal and extraneuronal distribution. The painkiller effect of opioids is induced by the synergy of the two events, namely reduction of pain threshold and emotional detachment from pain. The opioid effects transcending analgesia include sedation, respiratory depression, constipation and a strong sense of euphoria. There are opioid-like substances endogenously produced by the body. Naturally occurring peptides, called enkephalins, have opioid-like activities but are not derived from opium and exert opioid-like effects by interacting with opioid receptors on cell membranes. Yet, animals do contain the same morphine precursors and metabolites as opium poppy and are able to synthesize endogenous morphine alkaloid. Experimental and clinical studies show that opioids, at doses comparable to those of endogenous opioids, can activate pronociceptive systems, leading to pain hypersensitivity and short-term tolerance, a phenomenon encountered in postoperative pain management by acute opioid administration. Whether endogenous opioids play a role in the acute pain necessary to the survival of the individual, remains an open question.

KEY WORDS: opioids; morphine; analgesia; pain.

Pert and Snyder were able to identify for the first time the bond between radioactive opioids and receptors in a mixture of rodent brain and distinguish specific opioid-receptor interactions from non-specific binding between opioids and brain membranes (1). These researchers investigated the molecular structures nearby the recognition site in the same brain membrane, to identify the second messenger that could convert the information related to the recognition of the receptor by the opioid into changes in the cell function. This second messenger was established as the cyclic adenosine monophosphate (cAMP) whose concentration levels are governed by an enzymatic machinery that uses the sodium ion. When opioid agonists bind to the proper receptor, a change occurs in the key interactions that sodium has with the apparatus of cAMP. Obviously, antagonists bind with equal affinity to the receptor but do not cause changes although they are able to reverse the effects of opioids (1). The opioids exert their lethal effect by depressing respiration. Patients in overdose may return to normal conditions even if they are in a deep and presumably irreversible coma, when subjected to an injection of a small amount of intravenous naloxone, an opiate antagonist able to remove all the molecules by their respective opiate receptors (1).
The discovery that opioids were acting through specific receptors, inducing changes in the cAMP, was not sufficient to clarify why they abolish pain and give a feeling of well-being and sometimes euphoria. The step forward was taken when opiate receptors were localized in the brain (2). A highest density of opioid receptors was located in areas known to be involved in integrating information regarding pain. Signaling triggered by pain impulse is transmitted to the spinal cord through sensory nerves that communicate with the neurons of the spinal cord. Some nerves are long and protrude towards the brain. Other ones are small and dialogue with the gelatinous substance of the spinal cord where a high density of opioid receptors is localized. Another area with a high concentration of opiate receptors is the medial thalamus that filters incoming sensory information associated with intense and deep pain, sending messages to the cerebral cortex. This last is the type of pain excellently relieved by opioids (3, 4).

Analgesic effect

There are three major classes of opioid receptors that mediate distinct effects: mu (μ), delta (δ) and k (κ) (5). All these receptors mediate spinal analgesia. Particularly, μ opioid receptor subtype 1 mediates also supraspinal analgesia.
The opioid receptors are coupled to inhibitory G proteins (6). The receptor activation has many consequences, including inhibition of adenylate cyclase with reduced generation of cAMP and other second messengers. Opioids increase the conduction of potassium and hyperpolarize target cells making them less responsive to depolarizing pulses and inhibiting calcium influx. These actions reduce the release of neurotransmitters from neurons and decrease the generation of the postsynaptic impulse. The analgesic effect of opioids is

the result of a complex series of neuronal interactions. At supraspinal level, opioid analgesics bind to μ receptor located on GABAergic neurons. Usually, these neurons project to the descendant inhibitory neurons of the brainstem and inhibit them. Inhibition of GABAergic neuron induced by binding of opioid analgesics to opioid receptor, allows the activation of descendent inhibitory serotoninergic neurons and finally produces analgesia. At spinal level, analgesic effect is produced by inhibiting the release of mediators of pain pathway such as substance P, glutamate and nitric oxide from nociceptive afferent neurons (7).

Morphine, heroin, fentanyl, codeine and dihydrocodeine are analgesic opioids acting as full-agonists a μ receptor and have a weak agonist activity at δ and κ receptors. Buprenorphine is a partial agonist at the μ receptor and also exert antagonistic activity at μ receptor; this last action will enhance μ mediated analgesia. Meptazinol is an analgesic opioid agonist at the μ receptor showing also agonist activity on muscarinic acetylcholine receptors. Tramadol and methadone are agonists at μ receptors and also inhibit the neuronal reuptake of norepinephrine and serotonin enhancing their analgesic activity. Methadone, in addition to its effect via the μ receptor, is also a glutamatergic NMDA receptor antagonist, action that can further inhibit the transmission of pain (8, 9).

Opioids alleviate pain at the spinal level by raising the threshold. If an individual is treated with morphine, he will experience pain in the presence of a painful stimulus more intense as compared to the one in the absence of morphine (10). However the main analgesic effect of opiates is not only an increase in the threshold of pain but also an attenuation of the subjective evaluation of pain. Patients treated with morphine because of excruciating pain, relate pain without trouble associated with it. They have a conscious response to pain, whereas this response is modified at higher brain levels (11). The impressive abundance of opiate receptors in the limbic system suggests an explanation for the emotional changes caused by opiates. The limbic system, a set of different structures located immediately below the cerebral cortex, contains the highest opioid receptor accumulation than other parts of the brain (12). The limbic system has nerve connections with many other parts of the brain such as the hypothalamus which in turn is closely connected with hypophysis and therefore capable of influencing the hormonal secretion. Otherwise, other nuclei of the brain such as the locus coeruleus, which contains an extremely high concentration of opioid receptors, send networks of nerve endings to the limbic system (13).

Opioids cause also constriction of the pupil and the pupil pinpoint indicate a powerful, easily visible effect produced by opioids (14). The pupil diameter is regulated by different brain districts present in the brainstem some of which, particularly the pretectal nucleus, are rich in opioid μ and κ receptor subtype. Numerous groups of nerve cells in the brainstem are involved in the regulation of respiratory activity and one of the main area that control respiratory reflexes, the nucleus of the solitary tract, has a high concentration of μ2 subtype and δ opiate receptors (15). Stimulation of μ and κ receptors in neuronal plexus of the gut wall induces an increase in the resting tone of the intestinal wall and sphincter. Increased segmentation activity and decreased propulsive activity was observed in intestine and large intestine following opioid administration. Therefore, opioid therapy is associated with constipation and a high percentage of those who take opioids will have to resort to laxatives (16).

Endogenous opioid peptides

The brain produces different endogenous opioid peptides which are neurotransmitter agents through specific opioid receptors (17). Hughes and Kosterliz have isolated and successfully analyzed brain material with structure similar to opioids and identified it as a mixture of two small peptides each containing only five aminoacids of which four were exactly the same in both. The two researchers have called them enkephalins from the greek words *en* (in) and *kefalè* (head). Each of these pentapeptides contains the aminoacid sequence Tyr-Gly- as messenger domain linked to leucine and methionine and they are called leu-enkephalin and met-enkephalin. Other agonists, containing the same aminoacid sequence, are dynorphins A and B and a peptide of 31 aminoacids with a met-enkephalin to its carboxyl termination which is the most potent agonist beta-endorphin (18). Two additional peptides endomorphin 1 and 2 have been recently identified to have a sequence in the domain messenger Tyr-Pro. The various endogenous opioid peptides show preferential receptor binding. The beta-endorphins bind equally to the μ and δ receptors. Endomorphins bind largely but not exclusively to μ receptors (19). Dynorphins bind preferentially to δ receptors. Enkephalins bind primarily to the κ receptors. The different physiological effects elicited by these receptors are due to their specific neuronal distribution. Enkephalinergic derivatives definitely have painkiller effects though derivatives produced by pharmaceutical companies were dramatically less efficacious than morphine.

Yet, the picture of endogenous opioids should be completed with endogenous alkaloid morphine. Studies have demonstrated that animals do contain the same morphine precursors and metabolites as opium poppy. Morphine alkaloids in animal tissues were first demonstrated by immunological recognition. The molecular structure of the HPLC purified compound was confirmed as morphine by liquid and gas chromatographic retention times and mass spectrometry in various normal tissues such as rat and rabbit skin, mouse, bovine and primate brain, hypothalamus and adrenal glands, invertebrate and human tissues, mammalian lung and human plasma, human cerebrospinal fluid (20).

Why there are such a number of different endogenous neurotransmitters as opioid receptor ligands is a question that has yet no answer.

Paradoxical effect of morphine

Surprisingly, morphine administration at very low doses induces a paradoxical effect, namely pain threshold is decreased inducing hyperalgesia. Experimental and clinical studies show that opioids can activate pronociceptive systems, leading to pain hypersensitivity and short-term tolerance, a phenomenon encountered in postoperative pain management by acute opioid administration (21-23).

Classically, morphine at analgesic dose activates G inhibitory protein coupled to opioid receptors to inhibit adenylyl cyclase activity and decrease neuronal cAMP levels. However, some studies suggest that opioids can exert stimulatory effects either at doses well below those producing neuronal inhibition or after chronic exposure. In cultured dorsal root ganglion neurons, nanomolar concentrations of opioid agonists increase action potential duration, whereas micromolar concentrations produce the opposite effect (24). This dual

action of opioids has been explained on the basis of a bimodal opioid receptor model where ultra-low doses of an opioid agonist activate a Gs-coupled excitatory mode of the opioid receptor to activate adenylyl cyclase and increase neuronal excitability. Another study *in vivo* demonstrates the presence of a nociceptive inositol signaling pathway stimulated by low concentrations of morphine, through μ receptor (25).

Conclusion

Opioids therefore have a bimodal action. They induce an excitatory action at lower doses which might be compared to concentrations that endogenous opioids have in human body. At high doses, the inhibitory effect of exogenous opioids in physiological systems exerts its effects achieving and also transcending analgesia. Naturally, pain has an important and inescapable role and is necessary to the survival of the individual. Endogenous opioids might have this role and function. If the perception of pain is a good sign of danger and warns us of what is wrong, pain accompanying acute and chronic diseases demands prompt resolution. In these situations, pain can and should be eased, without fatalism about its necessity.

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