

Analgesic Tolerance to Opioids

For the past 15 years, the World Health Organization has recommended morphine as the analgesic of choice for treatment of moderate to severe cancer pain.¹ Additionally, morphine and related opioids are widely used to alleviate moderate to severe pain after surgery or trauma, or with medical illness such as heart attack. Patients with apparently similar pain states have large differences in opioid dosing requirements. Factors that contribute to this marked variability include psychosocial status, type of pain (nociceptive, inflammatory, neuropathic, or mixed) and its severity, concurrent medications, gender and other genetic aspects, and whether patients are opioid-naive or tolerant. Although this issue of *Pain: Clinical Updates* focuses on analgesic tolerance, it is now clear that the biology of analgesic tolerance has much in common with mechanisms thought to produce and maintain pathological pain.²⁻⁴

Definition of Analgesic Tolerance

Tolerance is the phenomenon whereby chronic exposure to a drug diminishes its antinociceptive or analgesic effect, or creates the need for a higher dose to maintain this effect. In other words, the tolerant organism is less susceptible to the pharmacological effects of a drug as a consequence of its prior administration.⁵ Clinically, this definition assumes no progression in the disease state.⁶ In animal studies, antinociceptive tolerance is readily induced: even a few days of administration of an opioid such as morphine results in a progressive loss of its antinociceptive effect. As a result, the dose-response curve in opioid-tolerant animals shifts toward the right relative to that for opioid-naive animals (Fig. 1).

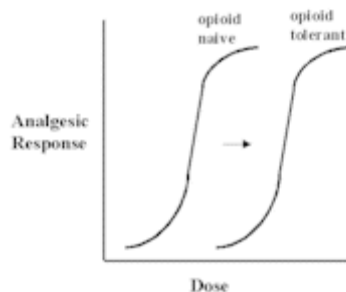


Fig. 1. Rightward shift in the opioid dose-response curve in opioid-tolerant animals relative to opioid-naive animals.

Analgesic Tolerance in Patients

For certain nonanalgesic actions of opioids such as respiratory depression, somnolence, or nausea, the onset of tolerance is often prompt. By contrast, little or no clinical tolerance develops for opioid-induced constipation,⁷ and proactive bowel care is necessary upon commencing chronic opioid treatment.

Increases in opioid dosing requirements during cancer pain may herald disease progression rather than true pharmacological tolerance.⁷ Indeed, most authors report no escalation of morphine dose requirement in such patients unless pain intensity increases.^{6,8-11} Additionally, clinical surveys of the long-term use of opioids in chronic noncancer pain¹²⁻¹⁴ indicate that pharmacological tolerance is not a significant determinant of opioid dosing requirements.

Intriguingly, a recent study in patients without pain who received methadone as treatment for opioid dependence found marked tolerance to the analgesic actions of methadone, as well as pronounced cross-tolerance to morphine.¹⁵ The higher opioid requirements of highly tolerant patients treated for pain increase the likelihood of unpleasant nonanalgesic side effects due to greater circulating concentrations of opioids and potentially toxic opioid metabolites.^{16,17} Rather than increasing the dose of morphine to compensate for the high degree of cross-tolerance to morphine when analgesia is desired in methadone maintenance patients, an alternative is to rely on a nonopioid or an opioid that produces pain relief through a mechanism distinct from that of morphine or methadone. Although it is widely viewed as producing analgesia through the μ -opioid receptor, evidence from our laboratory indicates that oxycodone is also a κ -opioid analgesic.¹⁸ Indeed, the recent finding that rats rendered tolerant to intravenous morphine completely lack cross-tolerance to intracerebroventricular (i.c.v.) oxycodone¹⁹ suggests that oxycodone may be suitable for methadone maintenance patients at times when they require strong opioid analgesia.

"Lack of Tolerance" in Cancer Pain versus "Marked Tolerance" in Methadone Maintenance

One possible explanation for the dichotomy between the apparent lack of opioid analgesic tolerance in patients with persistent pain states versus the marked tolerance found in methadone maintenance patients¹⁵ is that persistent pain itself may activate "antitolerance" mechanisms. Another possibility is that one or more of the nonopioid adjuvant medications commonly taken by patients with persistent pain due to nerve or tissue injury may inhibit the cellular mechanisms responsible for the development of analgesic tolerance. Indeed, mechanisms that underlie the establishment and maintenance of persistent pain states appear to overlap with those proposed for morphine tolerance.^{2,4} These mechanisms include: (1) an increase in the sensitivity of the N-methyl d-aspartate (NMDA) receptor,^{2,4} (2) an increase in spinal cord concentrations of dynorphin A,⁴ and (3) a decrease in the responsiveness of the μ -opioid receptor.⁴

Morphine-3-Glucuronide (M3G): Anti-analgesic and Neuroexcitant?

More than half of each dose of morphine given systemically to rats or humans is metabolized to an analgesically inactive metabolite, morphine-3-glucuronide (M3G). Thus, morphine can be regarded as a prodrug for M3G. In humans, a further 10% of each morphine dose is metabolized to morphine-6-glucuronide (M6G), a potent analgesic (Fig. 2).²⁰

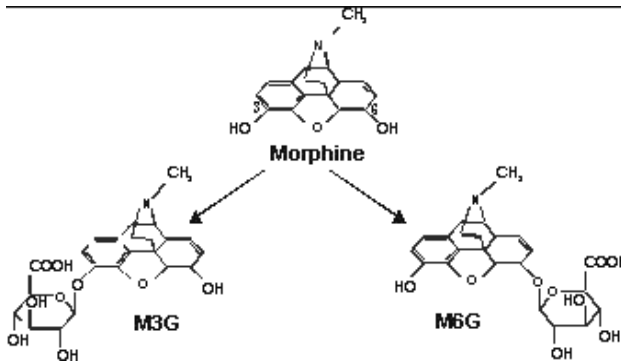


Fig. 2. Morphine is metabolized to morphine-3-glucuronide (M3G), an analgesically inactive metabolite, and morphine-6-glucuronide (M6G), a potent analgesic.

M3G's lack of pain-relieving effect is consistent with its lack of binding to opioid receptors.¹⁷ M3G is a potent neuroexcitant when administered by the i.c.v. route to rodents, evoking a range of excitatory behaviors including myoclonus, allodynia, wild-running, and seizures.¹⁷ I.c.v. administration of M3G attenuates the antinociceptive effects of i.c.v. morphine²¹ and i.c.v. M6G,²¹⁻²³ consistent with the view that M3G is an anti-analgesic. Indirect evidence in rats implicates M3G in the development of antinociceptive tolerance to systemically administered morphine.²⁴⁻²⁶ This view is supported by our recent studies using cultured fetal hippocampal neurons, showing that M3G indirectly activates NMDA receptors:²⁷ a common pathway with morphine tolerance. Thus, it is plausible that clinical analgesic tolerance to morphine may, at least in part, result from an increasing accumulation of M3G in plasma and cerebrospinal fluid relative to morphine and M6G.

NMDA-Receptor Cascade: Ca² Influx, PKC Translocation, and NO Production

Ca² influx. Indirect NMDA-receptor activation, whether produced by chronic morphine administration or nerve or tissue injury, increases Ca² influx into neurons. This influx is the key event responsible for subsequent translocation/activation of protein kinase C (PKC) from cytosol to cell membrane, increased intracellular NO production, and μ -opioid-receptor hyporesponsiveness (Fig. 3).

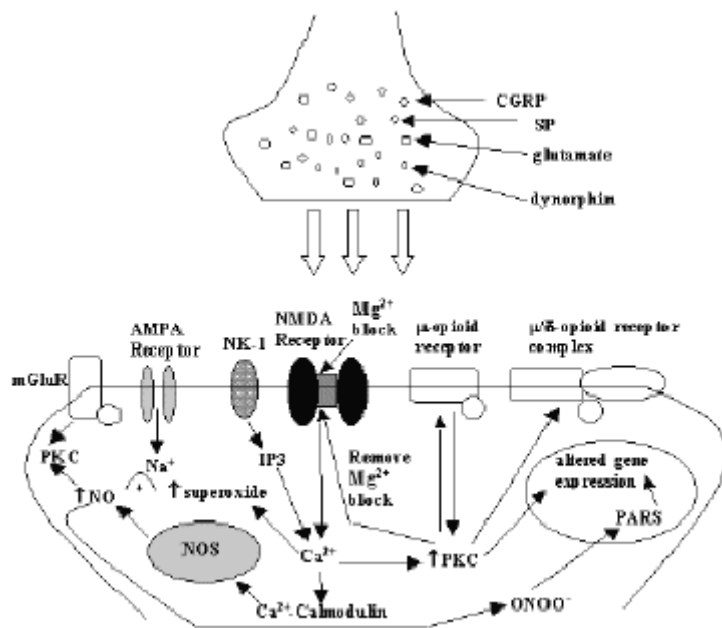


Fig. 3. Schematic representation of mechanisms common to the development of tolerance to the pain-relieving effects of morphine and the development of hyperalgesia secondary to nerve and/or tissue injury. Abbreviations: CGRP = calcitonin-gene-related-peptide; IP3 = inositoltriphosphate; mGluR = metabotropic glutamate receptor; NK-1 = neurokinin-1 receptor; NMDA = N-methyl-d-aspartate; NO = nitric oxide; NOS = nitric oxide synthase; ONOO⁻ = peroxynitrite; PARS = poly (ADP ribose) synthetase; PKC = protein kinase C; SP = substance P.

PKC activation. PKC is not a single enzyme, but comprises at least a dozen isoforms.²⁸ Of these, PKC γ is key to the development and maintenance of pathological pain states.^{2,29} PKC phosphorylates numerous receptors and ion channels, including the μ -opioid receptor and the calcium channel associated with the NMDA receptor. PKC-mediated phosphorylation of the NMDA receptor expels the Mg²⁺ ion that at rest blocks the Ca²⁺ channel. The unblocked channel no longer requires depolarization for activation,² resulting in a positive feedback loop of amplified NMDA-receptor responses and further activation of PKC.

Phosphorylation of the μ -opioid receptor by PKC may uncouple the receptor from its G-protein or alter the properties of its associated potassium channel.² In either case, the result is reduced responsiveness of the μ -opioid receptor to exogenous opioid drugs, i.e., tolerance. Interestingly, a recent study² has shown that activation of PKC decreases μ -opioid-receptor mRNA levels, suggesting that PKC also inhibits μ -opioid-receptor turnover. The relationship between this effect and opioid tolerance remains to be determined.

Administration of the GM1 ganglioside blocks both the translocation of PKC from cytosol to membrane and the development of analgesic tolerance to morphine. Additionally, GM1 ganglioside prevents the development of thermal hyperalgesia associated with morphine tolerance.³⁰ Gangliosides are thought to inhibit neuronal responses to excitatory amino acids such as glutamate, so ganglioside treatment could provide a new approach to prevention of opioid tolerance and management of hyperalgesia seen in neuropathic pain syndromes.

Activation of nitric oxide synthase (NOS). Three NOS enzymes have been cloned.^{31,32} The predominant form in the CNS is neuronal NOS (nNOS), subdivided into nNOS₁ and nNOS₂.^{33,34} Behavioral studies in rodents indicate that nNOS₁ (the predominant

supraspinal isoform) diminishes the antinociceptive actions of morphine, whereas nNOS₂ (the predominant spinal isoform) potentiates morphine antinociception. Nonselective NOS inhibitors, including NG-nitro-L-arginine (L-NNA), NG-monomethyl-L-arginine (L-NMMA), L-NG-nitro arginine methyl ester (L-NAME), and NG-nitro-L-arginine (L-NOARG), generally slow or block antinociceptive tolerance to morphine,³⁵⁻⁴⁶ suggesting that nNOS₁ plays an important role in this process.

Peroxynitrite formation. Influx of Ca²⁺ into neurons results in the production of superoxide from mitochondria. The simultaneous generation of NO and superoxide favors the production of peroxynitrite (ONOO⁻), a potent initiator of DNA strand breakage, which in turn initiates the activation of the nuclear repair enzyme, NO-activated poly-(ADP ribose) synthetase (PARS). Pronounced activation of PARS can result in cellular dysfunction and eventually a form of programmed cell death from impairment of mitochondrial respiration and depletion of cellular energy stores, and formation of so-called "dark neurons."³ The development of dark neurons in the dorsal horn of the spinal cord is associated with both morphine tolerance and nerve injury.³ Opioid metabolites such as M3G, hydromorphone-3-glucuronide (HM3G), and codeine-6-sulfate also have dose-related excitotoxic effects. All produce neuroexcitatory behaviors in rodents following i.c.v. administration,^{18,47} with steep dose-response curves suggesting cell death, although this requires experimental confirmation.

Spinal Dynorphin Release

Increased expression of dynorphin in the spinal dorsal horn is consistently observed following chronic opioid administration. Likewise, much evidence implicates spinal dynorphin in the development of enhanced nociceptive sensitivity^{48,49} that exaggerates antinociceptive tolerance to opioids.⁴ Although dynorphin A was originally identified as an endogenous antinociceptive and analgesic molecule (a κ -opioid agonist),⁵⁰ more recent studies indicate that dynorphin has significant pronociceptive activity that is not mediated by opioid receptors.^{4,51} Spinal administration of dynorphin antiserum (but not control serum) blocks the expression of abnormal pain behavior and the development of antinociceptive tolerance in rodents dosed chronically with opioids.⁴ Precisely how increased spinal dynorphin expression promotes pain and opioid tolerance is unclear.⁴ However, electrophysiological evidence indicates that dynorphin A₍₁₋₁₇₎ and its excitatory metabolites interact with a glycine-binding site on the NMDA receptor and with the glycine residues in positions 2 and/or 3.⁵² Another possibility is that dynorphin A and its excitatory fragments promote the presynaptic release of one or more nociceptive neurotransmitters such as glutamate, substance P, or calcitonin gene-related peptide (CGRP).⁴ Whatever mechanism is involved, therapeutic strategies to diminish dynorphin release in the spinal cord could enhance opioid analgesic sensitivity in pathological pain states and reduce the development of antinociceptive tolerance.

Anti-opioid Peptides

The antinociceptive effects of morphine are opposed by a number of endogenous peptides, termed anti-opioids, that are released in response to the administration of an opioid. Neuropeptides shown to have anti-opioid activity in behavioral studies in rodents include vasopressin, oxytocin,⁵³ nociceptin,^{54,55} neuropeptide FF (NPFF),^{56,57} and

cholecystokinin (CCK).⁵⁸⁻⁶¹ The precise contributions of each of these anti-opioids to analgesic tolerance remain to be clarified.

Opioid Receptor Involvement in Tolerance Development

Mu-opioid receptor. PKC is not the only enzyme capable of phosphorylation and desensitization of μ -opioid receptors. Two G-protein-coupled receptor kinases, β -adrenergic receptor kinase 2 and β -arrestin 2, also synergistically desensitize μ -opioid receptors.⁶² Furthermore, knockout mice that lack β -arrestin 2 display neither μ -opioid-receptor desensitization nor tolerance to the antinociceptive effects of chronically administered morphine.⁶² The relationships between the latter two mechanisms and PKC remain to be determined.

Delta-opioid receptor. Several studies indicate that activation of the δ_2 opioid receptor subtype is required for the development of both antinociceptive tolerance to morphine and supersensitivity (i.e., enhanced morphine potency following chronic antagonist exposure).⁶³⁻⁶⁶ For example, tolerance to the antinociceptive effects of morphine is attenuated in mice and rats by (1) naltrindole and naltrindole 5' isothiocyanate (5'-NT11), both selective agonists at the δ_2 opioid receptor; (2) i.c.v. administration of antisense oligonucleotides that inhibit expression of the cloned δ -opioid receptor (DOR-1); and (3) deletion for the gene for DOR-1 (i.e., knockout mice).⁶⁴⁻⁶⁸

Additionally, simultaneous administration of morphine at supraspinal and spinal levels produces antinociceptive synergy,⁶⁹ a phenomenon attributed to formation of a functional μ/δ -opioid-receptor complex.⁶⁹ However, this hypothesis requires confirmation in δ -opioid-receptor knockout mice.

Conclusion

Many distinct pharmacological agents attenuate or block the development of antinociceptive tolerance to morphine: NMDA antagonists, NOS inhibitors, substance P antagonists, CGRP antagonists, PKC inhibitors, Ca² channel blockers, and dynorphin antiserum. These diverse targets are interrelated components of a complex cascade, replete with parallel redundancies to ensure "fail-safe" signaling.⁷⁰ The initiating event(s) in the development of analgesic tolerance remain to be elucidated. One would expect, and clinical experience confirms, that patients with nerve injury require higher morphine doses because nerve-injury-evoked hyperalgesia mimics analgesic tolerance. Coadministration of "anti-hyperalgesic" adjuvant medications together with an opioid such as morphine would appear to be an attractive strategy to reduce analgesic tolerance and alleviate nerve injury pain, while reducing opioid-related neuroexcitatory side effects. Rigorous clinical trials will be required to translate preclinical findings and guide selection of "anti-hyperalgesic" adjuvant drugs in the clinic.⁷¹

Further study is needed to explain the dichotomy between the apparent lack of opioid analgesic tolerance in patients with persistent pain states versus the marked analgesic tolerance found in patients receiving methadone maintenance therapy¹⁵ or easily induced in preclinical studies of intact rodents. Methadone has weak,⁷² naloxone-reversible⁷³ NMDA-antagonist activity that appears to be overcome by NMDA activation during

chronic exposure to a μ -opioid agonist in the absence of pain. Whether pathological pain, such as that associated with cancer and/or nerve or tissue injury, activates an endogenous "antitolerance" mechanism remains to be addressed. Patients with chronic cancer or noncancer pain often receive multiple drugs for disorders related or unrelated to their pain. These other pharmacological agents may well affect the biochemical mechanisms of tolerance development. Improved drugs might forestall the development of analgesic tolerance while ensuring that the nociceptive signaling apparatus remains in its "normal" state. Much remains for future investigation.

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