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INVITED REVIEW

NMDA Receptor and Opioid Analgesic Tolerance

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ABSTRACT

Opioids, the wonderful analgesics, remain the mainstay in the clinical management of moderate to severe pain. However, development of analgesic tolerance and increase in pain sensitivity are some of the major concerns following opioid treatment. Studies suggest that NMDA receptor-mediated intracellular events play a role in mediating these effects. Moreover, NMDA receptor antagonists effectively prevent and gradually reverse opioid analgesic tolerance. Collectively, these studies unfold the involvement of NMDA receptor in opioid tolerance.

Keywords: NMDA Receptor, Opioid Tolerance.

INTRODUCTION

Opioids are the drug of choice for the clinical management of moderate to severe pain. Along with the known side effects, development of tolerance (diminution or reduction in the effect and potency of a drug after prolonged exposure) and dependence (constant need of the drug to prevent certain withdrawal symptoms) are corollary to opioid treatment. Over the past few years, several studies have documented the occurrence of abnormal pain sensitivity including *hyperalgesia* (exaggerated nociceptive responses to noxious stimulation) and *allodynia* (nociceptive responses to innocuous stimulation) in opioid treated animals. This concomitant opioid induced pain sensitivity is supposed to be closely linked to opioid tolerance. One of the series of efforts in studying the mechanism of tolerance has shown the involvement of excitatory amino acid (EAA) receptors such as the N-methyl-D-aspartate receptor (NMDA receptor) in opioid tolerance. [1] The NMDA receptor antagonists have been implicated in inhibiting dependence and tolerance to the antinociceptive effect and sensitization to locomotor effect following prolonged morphine administration. [2-3] This paper throws light on explaining the mechanism of morphine tolerance taking account of two most important systems in nociception and antinociception: The NMDA and opioid receptor system, and the role of NMDA receptor antagonists in opioid tolerance.

OPIOID AND NMDA RECEPTORS: CNS DISTRIBUTION

Recently combined use of various techniques, like molecular biology, immunocytochemical and autoradiography receptor binding, has enhanced our knowledge about the location and distribution of opioid and NMDA receptors within the CNS. With the help of autoradiography receptor binding methods, NMDA receptors have been localized both in supraspinal (*hippocampus, cerebral cortex, thalamus, striatum, cerebellum and brain stems*) [4-5] and spinal (*substantia gelatinosa of dorsal horn and very low levels in spinal gray matter*) [6], levels in mice and rats. Immunochemical methods have shown the localization of μ-opioid receptors in CNS areas (cerebral cortex, limbic system, hypothalamus, thalamus, brainstem, laminae I-II of medullary and spinal cord dorsal horns and dorsal root of ganglia) [7] of rat. Comparison of distribution pattern shows a close relationship between opioid and NMDA receptors. A recent study has provided an evidence for co-localization of μ-opioid receptors and NMDA receptors in both presynaptic and post synaptic sites in the shells of nucleus accumbens. [8]

INTRACELLULAR EVENTS FOLLOWING NMDA RECEPTOR ACTIVATION

Two Ca^{2+} mediated intracellular events, initiated by NMDA receptor activation are of prime interest here, because of their involvement in CNS neuronal plasticity and opioid tolerance. These are cellular redistribution and activation of Ca^{2+} sensitive Protein Kinase C (PKC) and production of nitric oxide (NO).

GM 1 ganglioside, a reported intracellular PKC translocation and activation inhibitor both *in vivo* and *in vitro* [9], was found to abate thermal hyperalgesia induced by peripheral nerve injury. [10] Oppositely, SC-10, a PKC activity stimulator, could enhance formalin- induced hyperalgesia in rat. [11] Mayer *et al.,* 1995 found that spinal cord levels of membrane bound PKC increase reliably with morphine tolerance and intrathecal administration of GM 1 ganglioside abated the development of tolerance to the antinociceptive effects of morphine in rats. [12] Various studies have documented the involvement of NO in hyperalgesia induced by peripheral nerve injury [13], radiant heat [13] and intrathecal NMDA administration. [14] N^G -nitro-$_L$-arginine methyl ester, a NO synthase inhibitor, could effectively reverse the persistent thermal hyperalgesia. [15] In a study, co-administration of morphine and N^G -nitro-$_L$-arginine methyl ester prevented the development of tolerance to the antinociceptive effect of morphine. [16]

Collectively, development of neurogenic and inflammatory hyperalgesia and morphine tolerance is interlinked with the

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NMDA receptor-mediated intracellular PKC translocation/activation and NO production.

OPIOID ADMINISTRATION AND ACTIVATION OF NMDA RECEPTOR

Opioids have both presynaptic and postsynaptic inhibitory action within the spinal cord. However, there is evidence that activation of NMDA receptors is involved after exogenous morphine administration. The ability of morphine, inhibitory in nature, to activate NMDA receptor is difficult to envision. The interaction between the μ-opioid receptor and NMDA receptor could occur either within the same neuron or from a neural circuitry involving two or more neurons. [17] In a pioneer study providing insight into the interaction of NMDA and μ-opioid action, initially NMDA receptor, in trigeminal dorsal horn neuron preparation, in vitro, mediated depolarization was induced by glutamate and later it was shown that the magnitude of the depolarization was enhanced by the addition of exogenous μ-opioid agonist. Further they documented that activating and inhibiting PKC respectively enhanced and blocked the μ-opioid agonist induced depolarization of NMDA receptor [17] Subsequently, it was proven that PKC [12] is the prime intracellular component that mediates this opioid induced activation of NMDA receptor activation (by its endogenous agonist) by removing the Mg^{2+} blockade of NMDA receptor (a necessary step for the NMDA receptor activation) thereby suggesting that the NMDA receptor can be activated even in the powerful inhibitory action of opioids.

Post synaptic opioid receptor activation is mediated by exogenous ligand, i.e. morphine initiates GTP binding protein- mediated Protein Kinase C (PKC) translocation/activation which in turn causes removal of Mg^{2+} blockade of NMDA receptor. Thus now, even small amount of excitatory amino acid (EAA) ligand, which could release from presynaptic terminals of primary afferent fibers, could activate the NMDA receptor and allow localized Ca^{2+} channel opening. Raised intracellular Ca^{2+} levels activate additional PKC, production of NO via Ca^{2+} -calmodulin mediated activation of NO synthase and relevant gene expression. PKC then may modulate μ-opioid activated G-protein coupled K^{+} channels or uncouple G-protein from the opioid receptor. In addition, NO may activate various protein kinases via cGMP or NO may diffuse out from neuron and enhance presynaptic release of endogenous EAA. In this way the, exogenous opiates may increase the basal level of presynaptic release of endogenous EAAs.

NMDA RECEPTOR ANTAGONISTS AND OPIOID TOLERANCE

Repeated intrathecal morphine administration over 7 days period resulted in reduction of baseline nociceptive threshold in rats on paw withdrawal test. [1] In another study similar results were reported as reduction in baseline nociception threshold in animals on repeated heroin administration. [18] Progressive reduction of baseline nociceptive thresholds in above studies potentially depicts an increase in pain sensitivity after repeated opioid administration. In another study, opioid treated patient reported more pain than the matched non-opioid controls. [19] Collectively, these findings suggest that repeated opioid administration trigger two opposing cellular mechanisms i.e. *desensitization (opioid tolerance)* and *sensitization (activation of pronociceptive system)*.

In one study, intrathecal administration of NMDA receptor agonist (NMDA) evoked thermal hyperalgesia similar to that induced by peripheral heat injury in rats. [20] In another study, Intraperitoneal or intrathecal NMDA receptor antagonists (competitive, AP-5 and noncompetitive, MK-801) diminished thermal hyperalgesia to radiant heat in animal model of neuropathic pain. [21] There are some evidences for the involvement of same spinal cord locus in the both mechanisms i.e. hyperalgesia and morphine tolerance [23] These findings potentially address the role of NMDA receptor in hyperalgesia. It was found that co-administration of NMDA receptor antagonist with morphine prevented tolerance and dependence [22] More than a dozen studies have documented that co-administration of morphine with MK-801 prevent the development of morphine tolerance in rats, mice and guinea pigs. The summary of these experiments is listed below. [3]

- Morphine was administered subcutaneous, intravenous, intrathecal, intracerebroventricular, intraperitoneal or oral either as daily bolus or continuous infusion through osmotic pumps.
- Competitive (AP-5, LY235959, LY274614 and ACEA-1328) as well as noncompetitive (dextromethorphan, CPP and memantine) NMDA receptor antagonists were used in these studies.
- Behavioral tests employed in these studies included, hot-plate, tail-flick and formalin tests.
- Both mice and rats have been used in these studies and no reliable differences in species were reported in relation to NMDA receptor antagonists on morphine tolerance.

However, single treatment with NMDA receptor antagonist did not restore the antinociceptive effects of opioids in tolerant animals. Furthermore, it is important to note that these antagonists do not produce antinociception by themselves but potentiate the antinociceptive effect of morphine. [24] Both associative (constant presence of cue) and non-associative (lack of cue) components are involved in tolerance. One study [22] has shown that MK-801 was particularly effective in preventing non-associative tolerance as compared to that of associative tolerance.

SUMMARY

Tolerance and dependence are corollary to morphine treatment. Several studies support the role of EAA receptors (NMDA) in the morphine tolerance. Comparison of distribution patterns shows a close relationship between opioid and NMDA receptors in many CNS regions. Opioids have potential to modulate intracellular events mediated by NMDA receptors. Upcoming research in this field supports the role of PKC and NO in opioid tolerance and dependence. It is clear that reduced analgesia following repeated morphine administration could result from the development of both pharmacological tolerance to morphine analgesia and tolerance associated with induced hyperalgesia. NMDA receptor antagonists are found to effectively prevent and gradually reverse the tolerance to antinociceptive effect of morphine.

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