FORUM MINIREVIEW

Recent Advances in the Search for the μ -Opioidergic System

Preface

Minoru Narita¹ and Shinobu Sakurada^{2,*}

¹Department of Toxicology, School of Pharmacy, Hoshi University, Tokyo 142-8501, Japan

²Department of Physiology and Anatomy, Tohoku Pharmaceutical University, Sendai 891-8558, Japan

Opioid receptors are the primary sites of action for opioid alkaloids and endogenous opioid peptides, which have a wide variety of pharmacological and physiological effects. Morphine is the prototypical μ -opioid analgesic that serves as the standard drug against which all analgesics are compared in determining their relative analgesic potencies. Although several μ -opioid receptor (MOP-R) ligands including morphine, its metabolites, endomorphins (EMs), β -endorphin and dermorphin analogues share many pharmacological profiles acting through MOP-R, they also exhibit many differences. Recent behavioral studies have suggested the differential mechanisms of G-protein activation, antinociception and motivational effects induced by endogenous MOP-R ligands, endomorphin-1 (EM-1) and -2 (EM-2), and β -endorphin. Evidence for the existence of MOP-R subtypes has recently been confirmed by virtue of splicing events of the MOP-R gene. These findings indicate the possible existence of a multitude of distinct subtypes of MOP-Rs. The most significant advances within this field were discussed in the symposium on "Recent Advances in the Search for MOP-R Function," held at the 74th Annual Meeting of The Japanese Pharmacological Society (March 22, 2001; Yokohama).

James E. Zadina (Tulane University School of Medicine and Department of Veterans Affairs Medical Center, New Orleans, USA) reviewed **Isolation and Distribution of EMs in the Central Nervous System**. He and his colleague first isolated EM-1 (Tyr-Pro-Trp-Phe-NH₂) and EM-2 (Tyr-Pro-Phe-Phe-NH₂) from bovine and human brain. EMs exhibit the highest affinity and selectivity for the MOP-R of all known mammalian opioids. They are structurally distinct from the other endogenous opioid ligands such as β -endorphin, enkephalins and dynorphins. Both EM-1 and EM-2 show potent antinociceptive activity in a variety of animal models of acute and neuropathic pain. The EMs are implicated in the natural modulation of pain by extensive data localizing EM-like immunoreactivity

near MOP-Rs in several regions including primary afferents and their terminals in the spinal cord dorsal horn. In a nerve-injury model of chronic pain, a loss of spinal EM-like immunoreactivity occurs concomitant with the onset of chronic pain. The distribution of the EMs in other areas of the nervous system is consistent with an important role in the modulation of autonomic, neuroendocrine, and reward functions as well as modulation of responses to pain and stress.

Morphological Studies of the Endomorphinergic Neurons in the Central Nervous System were reviewed by Qing-Ping Wang et al. (Showa University School of Medicine, Tokyo, Japan; etc.). These include recent studies on the ultrastructure and synaptic relationships of EM-2 obtained by immunoelectron microscopic methods.

The Antinociceptive Properties of EM-1 and EM-2 in the Mouse were reviewed by Leon F. Tseng (Medical College of Wisconsin, Milwaukee, USA). Both EM-1 and EM-2 given intracerebroventricularly (i.c.v.) or intrathecally (i.t.) dose-dependently produced antinociception in mice. The antinociceptive effect induced by either EM-1 or EM-2 given i.c.v. or i.t. was selectively mediated by the stimulation of MOP-R, but not δ -opioid receptor (DOP-R) or κ -opioid receptor (KOP-R). Like other MOP-R agonists, both EM-1 and EM-2 given i.c.v. activate descending pain control systems by the releases of noradrenaline and serotonin in the spinal cord. However, the antinociception induced by EM-2 given i.c.v. or i.t. also contain an additional component, which is mediated by the release of Met-enkephalin and dynorphin A(1–17) acting on DOP2-R and KOP-R, respectively. These findings suggest that there are distinct subtypes of MOP-Rs which are independently involved in the EM-1- and EM-2-induced antinociception.

Differential Antinociceptive Effects Induced by Intrathecally-Administered EM-1 and EM-2 in Mice were reviewed by Shinobu Sakurada et al. (Tohoku Pharmaceutical University, Sendai, Japan). The i.t. injection of EM-1 and EM-2 produced a dose-dependent antinociception. Although pretreatment with naloxonazine, a selective MOP1-R antagonist, caused a dose-dependent suppression of the

*Corresponding author. FAX: +81-22-275-2013

E-mail: s-sakura@tohoku-pharm.ac.jp

antinociceptive effect induced by both EMs, the inhibitory effects by naloxonazine on the antinociception by EM-1 and EM-2 were somewhat different. A selective heroin/morphine-6 β -glucuronide antagonist, 3-methoxynaltrexone, blocked the i.t.-administered EM-2-induced antinociception without affecting the antinociception by EM-1. Additionally, the EM-2-induced antinociception was significantly attenuated by pretreatment with both DOP-R and KOP-R antagonists and i.t.-administered antisera against dynorphin A(1–17) and Met-enkephalin. These results suggest that the mechanism underlying i.t.-administered EM-2-induced antinociception is distinct from that of other MOP-R-ligands including EM-1.

EM-Induced Motivational Effect: Differential Mechanism of EM-1 and EM-2 was discussed by Minoru Narita et al. (School of Pharmacy, Hoshi University, Tokyo, Japan). An i.c.v. treatment with EM-1 produced the MOP-R antagonist-reversible rewarding effect, whereas EM-2 exhibited the aversive effect. The aversive effect was inhibited by not only β -funaltrexamine but also the KOP-R antagonist nor-binaltorphimine and antiserum against an endogenous KOP-R ligand dynorphin A(1–17). These findings clearly indicate the differential mechanism of the motivational effects by EM-1 and EM-2. Like the hypothesis proposed by Tseng and Sakurada, these findings provide further evidence for the indirect involvement of endogenous κ -opioidergic system in the EM-2-induced pharmacological actions.

Hirokazu Mizoguchi et al. (Medical College of Wisconsin,

Milwaukee, USA; etc.) focused on **Differential Mechanism of G-protein Activation Induced by Endogenous μ -Opioid Peptides, EM and β -Endorphin**. Although β -endorphin exhibits the strongest actions among endogenous opioid peptides mainly through the MOP-R, it also shows the distinct pharmacological actions from EMs. The MOP-Rs belong to the superfamily of seven-transmembrane domain receptors that are coupled to G-proteins. They clearly described the differential mechanism underlying G-protein activation induced by EMs and β -endorphin using [35 S]GTP γ S binding assay. EM-1 and EM-2 significantly attenuated the G-protein activation induced by β -endorphin in the mouse spinal cord. Considering the endogenous μ -opioidergic system, it is likely that EM-1 and EM-2 can negatively modulate the physiological overshooting of μ -opioidergic system induced by β -endorphin.

Concluding remarks. The existence of several exons in genes encoding MOP-R can provide the scope for additional diversity by virtue of splicing events. A considerable amount of evidence indicates a certain difference among endogenous μ -opioid peptides including EMs and β -endorphin. This may result from the splicing variant-dependent MOP-R subtypes. Further studies on the identification of the MOP-R subtypes for each endogenous μ -opioid peptides may provide valuable information to further our understanding of the physiological function of the endogenous μ -opioidergic system and pave the way for new therapeutic strategies for the control of pain.