Edomorphins and Dorsal Horn

Opioid receptors, which appear to be all G-protein coupled, can be divided into at least four well-defined types: μ, δ, κ, and ε. Enkephalins are considered to be the endogenous ligand for δ-opioid receptors, dynorphin for κ receptors and β-endorphin for ε receptors. Recently, two tetrapeptides, endomorphin (Endo) 1 and 2 were isolated from mammalian brain tissues and proposed to be the endogenous ligand for μ receptors [9, 29]. Here, Dun et al. [5] reported that endorphins, endomorphin (Endo) 1 and 2 were isolated from previously described endogenous opioid peptides have been shown to have high specificity and affinity for the μ-opioid receptors, a member of the G-protein-linked receptor superfamily [16, 29]. In this issue, Narita et al. [20] present findings indicating that both endomorphin-1 and -2 stimulate G-proteins by selective activation of μ-opioid receptors in the mouse periaqueductal gray matter. These findings provide evidence to support that endomorphin-1 and -2 act as partial agonists for μ-opioid receptors.

Pharmacology of the Nociceptin Receptor

Since the discovery of a novel opioid receptor-like orphan receptors (ORL1) [19], a heptadecapeptide, orphanin FQ or nociceptin (OFQ1N) was identified as its endogenous ligand [22]. Although several putative ORL1 antagonists, e.g. [Phe\(^{1}\) ψ (CH\(_{2}\)-NH)Gly\(^{2}\)] nociceptin-(1-13)-NH\(_{2}\) (Phe ψ), naloxone benzoylhydrazine (NBZ), acetyl-RYYR1K-NH\(_{2}\), and nocistatin, have been reported [7], their mode of action remains elusive. Chiou [3] reported that none of the putative ORL1 antagonists as listed above could be considered as specific and potent antagonist for the ORL1 receptors as measured from the inward rectifier activation in the periaqueductal gray neurons. These observations point to the urgent need for the development of a new generation of ORL1 antagonists.

Opioid and Central Itch

Itch is one of the most common adverse effects of opioid medication [1]. Although opioid antagonists such as naloxone are effective in suppressing certain kinds of morphone-induced itch or scratch, they have little effect on scratching induced by intrathecal morphine [28], suggesting that there may be several mechanisms of pruritogenic action of opioids. One of the mechanisms was reported in this issue by Kurokawa et al. [15] who have demonstrated the involvement of central μ-opioid receptors in opioid-induced scratch/itch.

Endomorphin Inhibition of Transmitter Release in the SG

Endomorphin-1 and -2 (Endos) are two peptides recently isolated form bovine and human brain and proposed as the endogenous ligands for μ-opioid receptors [9, 29]. It has been shown that Endos hyperpolarize membrane potential [26], activate inwardly rectified K\(^{+}\) currents [6] and block voltage-dependent Ca\(^{2+}\) current [4]. However, it is not clear whether Endos reduce synaptic transmission by pre- or postsynaptic mechanism. Here, Yajiri and Huang [27] reported that in addition to presynaptic actions on interneurons, Endos also inhibit evoked EPSC, by reducing transmitter release form A δ-afferent terminals.

Reduction in Inflammatory Neurotoxicity by Dynorphins

Although dynorphins are best known for their role in nociceptive/analgesic systems, recent studies suggest that dynorphins have diverse functions, including an effect on respiration, immunoregulation and NMDA receptors [2, 25]. Furthermore, dynorphins have been demonstrated to inhibit lipopolysaccharide (LPS)-induced production of nitric oxide and proinflammatory cytokines in mouse glia without the participation of k-opioid receptors [13]. In this issue, Kong et al. [14] reported that dynorphin (dyn) A-(1-8) significantly protected neurons against LPS-induced neuronal injury. A non-opioid dynorphin peptide, des-[Thyr\(^{1}\)]-dyn A-(2-17), also showed similar neuronal protection suggesting that these neuroprotective effects of dynorphins are not mediated through classical opioid receptors.

Opioids and Cholinergic Development

Opioid drugs such as methadone or buprenorphine are often used in the management of pregnant addicts. However, both human and animal studies indicate that perinatal opioid exposure produces a variety of neurobehavioral and neurochemical changes as well as leads to delays in the development of the nervous system [8, 12]. In this issue, evidence is presented to support involvement of nerve growth factor in the effect of opioids on cholinergic development [23]. These findings suggest that use of μ-opioid agonist or partial agonists in the management of pregnant women should be approached with care.
Acute Opioid Tolerance in Heroin δ Responding Mice

It is generally thought that the major pharmacological actions of heroin are due to the μ receptor action of its metabolites, 6-monoacetylmorphine (6MAM) and morphine [10, 11]. However, Randy and Fujimoto [21] reported here that upon intrathecal administration of morphine [21, 22] reported here that upon intrathecal administration in Swiss Webster mice, heroin and 6MAM act on δ receptors while morphine μ response is present. Combinations of morphine with the δ agonists produced tolerance to morphine which now acted through δ receptor (inhibited by i.c.v. naltrindole) indicating an unusual change in receptor selectivity for morphine.

PGi Stimulation and Behavior

Recently, Liu et al. [17] reported that electrical stimulation of nucleus paragigantocellularis (PGi) induces opioid withdrawal-like behavior in the rat. Maldonado [18] suggested that the PGi provides much of the extrinsic glutamatergic excitation to the locus coeruleus leading to hyperactivity of noradrenergic neurons there, a hallmark of opioid withdrawal. Currently, Rockhold et al. [24] present further evidence demonstrating mediation of these behaviors by glutamatergic neurotransmission within the locus coeruleus and discuss the involvement of putative excitatory opioid receptors in the behavioral effect of PGi stimulation.

References