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REVIEW

ENDOGENOUS MORPHINE AND ITS METABOLITES IN MAMMALS: HISTORY, SYNTHESIS, LOCALIZATION AND PERSPECTIVES

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Abstract—Morphine derived from *Papaver somniferum* is commonly used as an analgesic compound for pain relief. It is now accepted that endogenous morphine, structurally identical to vegetal morphine–alkaloid, is synthesized by mammalian cells from dopamine. Morphine binds mu opioid receptor and induces antinociceptive effects. However, the exact role of these compounds is a matter of debate although different links with infection, sepsis, inflammation, as well as major neurological pathologies (Parkinson's disease, schizophrenia) have been proposed. The present review describes endogenous morphine and morphine derivative discovery, synthesis, localization and potential implications in physiological and pathological processes.

Key words: morphine, morphine-glucuronide, dopamine, opioid receptor, analgesia.

Contents

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Abbreviations: 4-HPAA, 4-hydroxyphenylacetaldehyde; 4-HPP, 4-hydroxyphenylpyruvate; AADC, aromatic L-amino acid decarboxylase; COMT, catechol-O-methyltransferase; CSF, cerebrospinal fluid; CYP2D6, cytochrome P450 2D6; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOR, delta opioid receptor; EM, endogenous morphine; EMM, endogenous morphine metabolites; HPLC, high-performance liquid chromatography; KOR, kappa opioid receptor; M3G, morphine-3-glucuronide; M3S, morphine-3-sulfate; M6G, morphine-6-glucuronide; M6S, morphine-6-sulfate; MAO, monoamine oxidase; MD2, myeloid differentiation protein 2; MLC, morphine-like compound; MOR, mu opioid receptor; MS, mass spectrometry; NCS, norcoclaurine synthase; PNMT, phenylethanolamine N-methyltransferase; RIA, radioimmunoassay; TH, tyrosine hydroxylase; THP, tetrahydropapaveroline; TLR4, toll-like receptor 4; TYDC, tyrosine decarboxylase; TyrAT, tyrosine aminotransferase; UGT, UDP-glucuronosyl-transferase enzymes.

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GENERAL INTRODUCTION AND NOMENCLATURE

In the early 1950s, the presence of specific morphine-binding receptors was hypothesized on the basis of morphine's analgesic effects. In the 1970s, three different receptors for opioid and opiate compounds were discovered: the Mu (μ), Delta (δ) and Kappa (κ) opioid receptors (MOR, DOR and KOR, respectively) (Pert et al., 1973; Pert and Snyder, 1973). More recently, a fourth opioid receptor named nociceptin/orphanin FQ (NOR) was cloned. These opioid receptors have seven transmembrane domains coupled to G proteins (for review: Kieffer and Evans, 2002, 2009; Trescot et al., 2008; Dietis et al., 2011; Al-Hasani and Bruchas, 2012; Feng et al., 2012).

The presence of opioid receptors has led to the characterization of several endogenous ligands called opioids due to their peptidic nature: enkephalins (Hughes et al., 1975a,b; Simantov and Snyder, 1976), β-endorphin (Bradbury et al., 1976; Graf et al., 1976; Lazarus et al., 1976; Li and Chung, 1976; Li et al., 1976), dynorphin (Cox et al., 1975; Goldstein et al., 1979; Lowney et al., 1979), nociceptin/orphanin FQ (Meunier et al., 1995; Reinscheid et al., 1995) and endomorphins (Hackler et al., 1997; Zadina et al., 1997). In addition to endogenous opioid peptides, endogenous morphine-like molecules, which are known as endogenous opiates due to their alkaloid nature have been discovered (Gintzler et al., 1976a,b; Blume et al., 1977; Shorr et al., 1978). Nevertheless, these molecules remain unfamiliar to most scientists, with only a small number of laboratories focusing on this particular research area. The data on endogenous opiates are scattered among the thousands of articles on "exogenous morphine" and endogenous opioid peptides. Furthermore, confusion arises when scientists use the term "opiates" instead of "opioids" for endogenous opioid peptides. Because no clear consensus exists, the following conventions will be used in this review: "opioids" will refer to peptides having an affinity for opioid receptors, whereas "opiates" will refer to natural or synthetic morphine-derived alkaloids (morphine, codeine, morphine-glucuronides…).

The present review summarizes the findings from the available literature on endogenous opiates (endogenous morphine and endogenous morphine metabolites). Their history, synthesis in mammals, tissue/cellular localization and potential functions in physiological and pathological states will be addressed in the following paragraphs. We will also discuss exciting fundamental and therapeutic perspectives that have recently emerged from cutting-edge research.

Endogenous opiates: a history of their discovery

Discovery of endogenous morphine-like compounds. In 1903, the French scientist Dr. Mavrojannis made the observation that morphine injections in rats led to symptoms related to catalepsy and subsequently hypothesized that such symptoms in mammals are the consequences of endogenous "morphine-like" compounds (Mavrojannis, 1903). In 1970, Davis and Walsh (1970) were the first to propose the presence of "true" morphine in mammals that potentially arose from a synthetic pathway similar to the biosynthetic pathway described in plants. Around the time of the discovery of the first endogenous opioid peptides, the group of Pr. S. Spector demonstrated the existence of an endogenous non-peptide "morphine-like compound" (MLC) (Gintzler et al., 1976a,b, 1978). This MLC was detected in rabbit and cat brains using a radioimmunoassay (RIA) directed against morphine. Once extracted, this compound displayed pharmacological properties identical to those of morphine. Furthermore, this MLC, which bound opioid receptors, was resistant to peptidase/protease treatments (Gintzler et al., 1976a,b, 1978). In parallel, other studies described the presence of a MLC in guinea-pig blood and small intestines (Schulz et al., 1977) as well as in human blood (Pert et al., 1976). A year later, Blume et al. (1977) described an anti-morphine antibody that was able to bind specifically to MLC; the fact that it did not interfere with endogenous opioid peptides ruled out any possible artifacts. This group postulated that MLC has a molecular structure similar to that of morphine and hypothesized the existence of two families of compounds (peptide and non-peptide) that bind opioid receptors. The presence of MLC was described in the mouse brain and immunolocalized in neuronal perikarya and processes of the cerebellum and the raphe nuclei (Gintzler et al., 1978). Its presence was also described in the cerebrospinal fluid (CSF), urine and brain extracts of patients naïve for exogenous morphine or morphine derivatives, suggesting its endogenous origin (Shorr et al., 1978; Wuster et al., 1978). In 1981, Killian et al. (1981) confirmed the existence of a non-peptide compound immunoprecipitated by anti-morphine antibodies in the calf brain, with an analgesic activity that could be blocked by naloxone, an opioid receptor antagonist.

Identification of endogenous opiates. In 1985, Goldstein and collaborators described the presence of four different MLCs in the bovine brain and adrenal gland. Using a NMR (nuclear magnetic resonance) approach, they demonstrated that one of the four MLCs was structurally identical to morphine extracted from poppies (Goldstein et al., 1985). Morphine endogenously present in mammals was named "endogenous morphine" (EM) as opposed to morphine from plants (exogenous morphine). The same group subsequently described in the bovine hypothalamus, the presence of endogenous codeine, a morphine precursor (Weitz et al., 1986). In the years that followed, several studies focused on the presence of EM and endogenous codeine using high-performance liquid chromatography (HPLC), NMR and mass spectrometry (MS) approaches in tissues from different species (for review: Meijerink et al., 1999; Stefano et al., 2000).