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Rethinking the opiate system? Morphine and morphine-6-glucuronide as new endocrine and neuroendocrine mediators

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C Statistical Analysis
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Summary

Since the 80s, intrigued by presence of morphine precursors in some mammalian cells, different laboratories were able to characterize morphine and morphine precursors in animal tissues Endogenous morphine studies continued during 90s and this alkaloid was successfully characterized from more organs and fluids of vertebrates, including brain, adrenal gland, heart, cerebrospinal fluid and urine. Then, in the last three years a high rate of publications dealing with this topic emerged, leading to a better understanding of the endogenous morphine system. In this regard, this article comment all the new data recently collected on this rising subject and replace the morphine and its derivative, morphine-6-glucuronide, in the mammalian physiology.

key words: **Endogenous Morphine • M6G • opiate • PEBP • RKIP • Pain**

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Opium has long been associated with human history. Thus, a Persian physician used it for cough, anemia and diarrhea[1]. These medicinal properties are mainly due to morphine[2] which corresponds to one of the 40 alkaloids present in opium. After its discovery at the end of the XIX century, morphine was extensively used in hospitals for pain management and today it is still the most used analgesic substance (for review [1]). Exogenously administered morphine is catabolised in the liver by the UDP-glucuronosyltransferase enzyme family (UGT)[3], leading to the formation of morphine-3-glucuronide (M3G, 90%) and morphine-6-glucuronide (M6G, 10%). M3G is totally inactive, whereas M6G appears surprisingly to display stronger analgesic activity than morphine and with much lower side effects (*i.e.*, nausea, respiratory depression; for review [3,4]). These catabolic products are cleared in urine and bile. Since it is known that M6G may have a greater affinity to the μ1 opioid receptor (responsible for analgesia) than to μ2 (responsible for respiratory depression), it suggests that exogenous morphine and/or endogenous M6G can offer benefits as systemic analgesic molecules (for review [4]). Thus, the potential of M6G was investigated and at this time this molecule is presently under Phase III trial in a post-operative pain study (CeNeS pharmaceutical, Cambridge, U.K.), highlighting its biological and medical potential.

On the basis of the historical belief that morphine was not present endogenously in animals, studies on the pharmacological properties of morphine and derived substances had focused on the effects of opioid peptides (e.g., met-enkephalin) and exogenous opiates. Endogenous opioid peptides were characterized, followed by the discovery of opioid receptors μ, δ and κ (for review [5,6]). It was shown that morphine could bind to the same receptors used by endogenous opioid peptides, in particularly μ (MOR1 gene), which contains 3 subtypes μ1, μ2 and μ3. Among these receptors, the μ3 [4,7], which is found on immune cell membranes, was characterized as specific for morphine. A specific receptor for M6G may also exist and again correspond to a splicing variant of the MOR1 gene (for review [4]).

The morphine biosynthesis pathway in poppy starts with tyrosine and continues with a condensation of dopamine and 4-hydroxyphenylacetaldehyde [8]. Then, several steps involving enzymatic or spontaneous rearrangements lead to morphine, but also M6G. At the beginning of the 1980s, intrigued by the presence of morphine precursors in some mammalian cells (*e.g.*, catecholaminergic cells), several groups emitted the hypothesis of the presence of endogenous morphine in mammals. Thus, they started to describe the presence of morphine and derivatives (reticuline, salutaridine, codeine, etc…) in various vertebrate tissues, including the nervous system (for review [1,8,9]). Nevertheless, these discoveries didn't generate enthusiastic waves of support. Was it due to skepticism (*e.g.*, suspicion of external contaminations, very low doses of endogenous alkaloids) or because it is hard to break the dogma that molecules, first identified in plants, could be present in mammals? Such, skepticism was, in part, ruled out by the discovery of the endocannabinoids in the 90s [10,11].

During the same time, endogenous morphine studies have been continued and endogenous morphine was successfully characterized from more organs and fluids of vertebrates, including brain, adrenal gland, heart, cerebrospinal fluid and urine (for review [1,8,12]). Morphine and morphine precursors were also found in invertebrates and parasites [13]. Then, very recently, several crucial steps were reached leading to a better understanding of the endogenous morphine system. A group was able to demonstrate that morphine can be formed by a multi-step biosynthetic route from tyrosine and dopamine in a human catecholaminergic cell line SH-SY5Y and in other cancer cells [14,15]. In addition, our group was the first to show that human primary polymorphonuclear cells were able to synthesize morphine and that this synthesis is finely regulated [16]. These advances led to the 1st International Endogenous Morphine meeting in January 2005, followed by the creation of the Morphine Research Society [17].

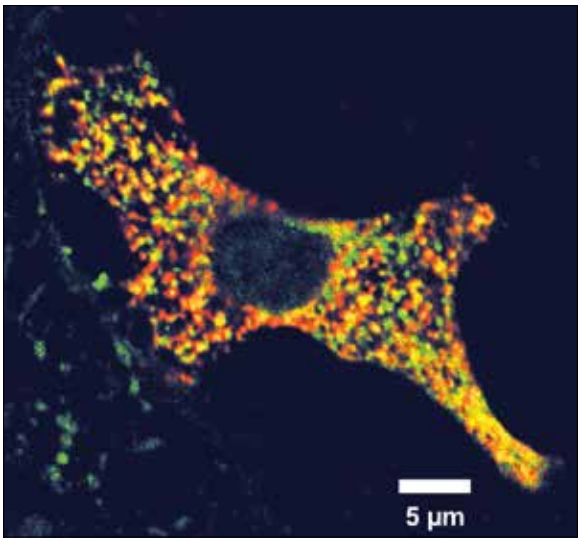

Figure 1. Immunolocalization of morphine-like components and chromogranin A in bovine primary cultured chromaffin cells. A double immunofluorescence confocal micrographs with an anti-chromogranin A antibody (an intragranular marker, in red) and anti-morphine-like molecules revealed (green) was performed and the colocalized immunolabellings were observed in yellow. For details see the article [18].

Interestingly, the poppy plant also contains M6G, which increases after the poppy capsule is allowed to sit for a long time. This year, our group has shown that M6G, is present in adrenal chromaffin granules (Figure 1) and secreted from chromaffin cells upon stimulation, indicating for the first time the neuroendocrine potential of such an endogenous alkaloid during stress situations [18]. It was also shown that endogenous M6G is not just a catabolism product but a true neuroendocrine mediator and that, in certain cells, the endogenous alkaloid synthesis pathway can reach a final step that is not morphine, but M6G. In addition, we were able to characterize the PhosphatidylEthanolamine-Binding Protein (PEBP, alternatively named Raf-1 Kinase Inhibitor Protein or RKIP) as an endogenous M6G-binding protein and to describe the unexpected presence of an UDP-glucuronosyltransferase 2B-like enzyme in chromaffin granule matrix. In the case of the chromaffin cells, once secreted into circulation, M6G may mediate several systemic actions based on its affinity for μ opioid receptors [4]. These activities were facilitated by PhosphatidylEthanolamine-Binding Protein, acting as a molecular shield and preventing M6G from rapid clear-

ance. It is important to point out that, in the case of chromaffin cells, it is easy to imagine a link with catecholamines that represent neuroendocrine mediators able to act on the peripheral and central nervous system on specific receptors.

Interestingly, a parallel can be made between endocannabinoids and endogenous opiates. Both are (*a*) present in plants [11], (*b*) act on specific receptors [19] and (*c*) finally display an implication in analgesia [20]. Thus, a synergistic analgesia with morphine was observed for the delta-9-THC (delta-9-tetrahydrocannabiol) [21,22]. Additionally, both types of signaling molecules can be coupled to constitutive nitric oxide release, influencing immune, vascular and neural activities [23].

Taken together, a clear picture of the biosynthesis morphinergic pathway appeared in animals: it starts with tyrosine and/or tyramine and ends with morphine or M6G. With all these new converging data, it appears that a true morphinergic system exists in mammals and that these endogenous alkaloids are involved in many physiological systems *via* specific receptors, opening a new way of thinking about the opiate system.

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