Pleiotropic Effects of Morphine-6β-glucuronide

FIRST isolated from opium in 1805 by Sertürner,[1] morphine is the oldest and still the most often used strong opioid analgesic. It is not a prodrug but has two major metabolites, morphine-3-glucuronide (M3G) and morphine-6β-glucuronide (M6G). Under certain circumstances, they contribute to the clinical effects of morphine. So far, their roles have been viewed as distinct, the 3-glucuronide being antianalgesic and excitatory and thus counteracting the effects of morphine, and the 6-glucuronide, in contrast, being a full μ-opioid agonist, roughly equipotent to morphine, and thus enhancing the analgesic and unwanted effects of morphine. In this issue of ANESTHESIOLOGY, van Dorp *et al.*[2] show that M6G can produce hyperalgesia. Moreover, this production is not mediated *via* opioid receptors because it is present in triple knockout mice lacking μ-, δ-, and κ-opioid receptors.

Because glucuronidation takes place at free hydroxyl groups, morphine undergoes glucuronidation at the third and sixth carbon atoms. The clearance of morphine to form M3G and M6G comprises 57.3% and 10.4%, respectively, and renal clearance comprises 10.9% of the total systemic plasma clearance.[3] The larger proportion of M3G formation is because aromatic hydroxyl groups serve much easier as conjugation recipients than do alicyclic hydroxyl groups (fig. 1). This is also why rats cannot form M6G, only M3G.

Both main morphine metabolites play their principal clinical roles when they accumulate as a result of decreased kidney excretory function. M6G is a μ-opioid agonist[4] and exerts analgesic activity.[5] Besides a contribution to chronic oral morphine analgesia,[6] the clinical role of M6G is seen mainly as increasing opioid side effects such as prolonged and profound sedation up to coma, especially in patients with renal insufficiency[7] or long-lasting respiratory depression during morphine therapy.[8] The respiratory depressive effects of M6G, however, are controversial. Results from classic and also modern opioid receptor pharmacology suggest that M6G, by having a lower affinity at μ$_2$-opioid receptors and a higher affinity at μ$_1$-opioid receptors than morphine[9] or by preferentially binding at certain μ-opioid receptor splice variants[10] up to the postulation of a
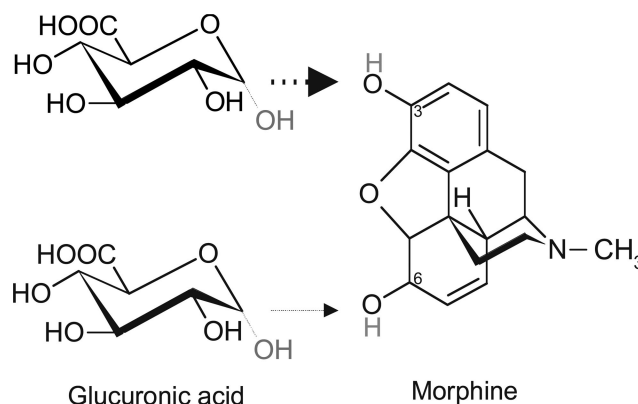

Fig. 1. Conjugation of glucuronic acid to the morphine molecule is preferentially at the third carbonic atom and in second line at the sixth carbonic atom. During conjugation, the *gray atoms* (H, OH) are set free.

distinct M6G opioid receptor,[11] may have decreased effects on respiration as compared with its parent. This has indeed been observed in humans[12] in an experimental setting, but contrasting interpretations of the role of M6G have also been reported.[13] Other side effects, such as greater emetic potency than morphine in rats,[14] have not always been observed, although M6G produced side effects similar to those of morphine when intravenously injected at equianalgesic doses.[5] To produce central nervous effects in humans, its dosing must be very high, exceeding the amount of M6G that is produced from an equianalgesic dose of morphine, or high and prolonged plasma concentrations must be maintained over time to allow for equilibration with the central nervous system. This is because of the difficulty of M6G in crossing the blood–brain barrier,[15] making it the opioid with the slowest first-order transfer half-life between plasma and a central nervous system effect site (2.9–16.2 h).[16] Acute analgesic effects, in contrast, are produced mainly in the periphery.[17]

Opposite effects, namely hyperalgesia and central nervous system excitation, have so far been associated with M3G rather than M6G. In animals, M3G produced seizures.[18] In humans, M3G has not yet been administered at high doses, but the injected amounts were close to those formed from analgesic doses of morphine, which might have been a reason for the absence of any effect.[19] When accumulating, M3G was presented as the cause for severe allodynia in a child, which disappeared after morphine administration was discontinued and the high M3G plasma concentrations had declined.[20]

A known clinical phenomenon with opioid use is the occasional appearance of increased pain sensitivity. This opioid-induced hyperalgesia was regarded as an opioid receptor–mediated effect,[21] was interpreted as a sign of opioid withdrawal,[22] and has been attributed to accumulation of the antianalgesic and excitatory M3G,[23] but has

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also been related to other mechanisms, such as glutamatergic signaling[24] with spinal glutamate transporter downregulation[25] or pathways involving β adrenoreceptors.[26]

Hyperalgesic effects of M6G in triple opioid receptor knockout mice clearly indicate that mechanisms apart from opioid receptors play a key role in this clinical phenomenon. Because morphine metabolites play an important role in its effects and morphine continues to be the basis of the therapy of severe pain, detailed knowledge about the complete pharmacodynamic effects is a prerequisite for optimizing pain therapy. A major step in elucidating the mechanism of unwanted opioid-induced hyperalgesia precedes finding a specific cure for it. The non-opioid receptor–mediated effects of M6G should also be considered in its development as an analgesic. Therefore, the accumulating knowledge about opioid receptor–mediated effects of different opioids and their active metabolites is completed by discoveries of clinically relevant effects that are not mediated *via* opioid receptors as the typical targets of opioids; thus, pleiotropic effects, such as previously shown G protein–independent effects of morphine on apoptosis,[27] extend to the active morphine metabolite M6G.

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