DIFFERENT DISTRIBUTION OF MORPHINE AND MORPHINE-6-GLUCURONIDE AFFECTS THEIR ANALGESIC EFFECTS
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Morphine, which is commonly used for the treatment of severe pain, is metabolized to an active metabolite of morphine-6-glucuronide (M6G) in humans. M6G is more potent than morphine by a factor of over 100 when administered intracerebroventricularly (i.c.v.), and by a factor of 2 – 4 if given systemically in rats. M6G has been shown to bind to distinct µ-opioid receptors that are not activated by morphine. However, the reason for more potent analgesic effect of M6G has not been clarified yet. We investigated CSF pharmacokinetics and analgesic effects of morphine and M6G after the subcutaneous (s.c.) injection of each drug in rats using a microdialysis method. Further, the distribution of morphine and M6G in central nervous system (CNS) was studied after the i.c.v. injection. The intrathecal CSF concentration of M6G was higher than that of morphine after the s.c. injection. Injection of morphine and M6G produced the dose-dependent suppression of formalin-evoked behavior. The analgesic effect of M6G was 3 – 4 times more potent than that of morphine, based on their s.c. doses. The analgesic potencies of morphine and M6G calculated from their CSF concentrations were very similar. After the i.c.v. injection, the apparent elimination clearance of M6G from the CSF was 10 times lower than that of morphine, and M6G was rapidly distributed into the intrathecal space. I.c.v.-injected M6G may activate both the spinal and supraspinal opioid receptors and produce synergistic increases in analgesia. These results suggest that morphine and M6G have similar analgesic potency based on their CSF concentrations. The CNS distribution characteristics of M6G may contribute to the potent analgesic effect after the i.c.v. injection.