분류번호	Ⅲ-P-53

LOW PERMEABILITY THROUGH THE BLOOD-BRAIN BARRIER OF MORPHINE GLUCURONIDES.

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The glucuronide conjugates of morphine have been claimed to exert significant neuropharmacological effects. Morphine-6-glucuronide (M6G) may be a potent opioid agonist *in vivo,* and morphine-3-glucuronide (M3G) may act as a weak opioid antagonist. The present study addressed the permeability of the blood-brain barrier (BBB) for these metabolites compared to morphine. Tracers were prepared by enzymatic glucuronidation of [N-methyl-^{3}H]-morphine. Brain uptake in rats was measured by the internal carotid artery perfusion technique and after i.v. bolus injections. In the perfusion experiments morphine showed a permeability-surface area product *(PS)* of 3.52 ± 0.61 μL min^{-1} g^{-1}. Uptake seems to be mediated by passive diffusion and was not saturable by 100 μM morphine in the perfusate. The BBB permeability of [^{3}H]-M3G and [^{3}H]-M6G was too low to be quantified after 5 min of perfusion. Brain uptake of [^{3}H]-M3G and [^{3}H]-M6G 60 min after i.v. bolus injection reached 0.0060 ± 0.0003 and 0.0030 ± 0.0005 % injected dose per g, respectively. From these brain concentrations and from the corresponding plasma concentration - time curves, BBB *PS* values of 0.14 ± 0.02 μL min^{-1} g^{-1} and 0.11 ± 0.01 μL min^{-1} g^{-1}, respectively, were calculated. The ratio of BBB *PS* values is complementary to the analgesic potencies of morphine and M6G after different routes of administration. The low *PS* of M6G explains, why it is approximately equipotent to morphine after systemic injection, although it is about 2 orders of magnitude more potent than morphine after administration directly into the central nervous system.