Morphine suppresses tumor angiogenesis through a HIF-1alpha/p38MAPK pathway.

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Source

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Abstract

Morphine, a highly potent analgesic agent, is frequently prescribed for moderate to severe cancer pain. In this study, morphine was administered at a clinically relevant analgesic dose to assess tumor cell-induced angiogenesis and subcutaneous tumor growth in nude mice using mouse Lewis lung carcinoma cells (LLCs). Implantation of mice with a continuous slow-release morphine pellet achieved morphine plasma levels within 250-400 ng/ml (measured using a radioimmunoassay, Coat-A-Count Serum Morphine) and was sufficient to significantly reduce tumor cell-induced angiogenesis and tumor growth when compared with placebo treatment. Morphometric analysis for blood vessel formation further confirmed that morphine significantly reduced blood vessel density (P < 0.003), vessel branching (P < 0.05), and vessel length (P < 0.002) when compared with placebo treatment. Morphine's effect was abolished in mice coadministered the classical opioid receptor antagonist, naltrexone, and in mu-opioid receptor knockout mice, supporting the involvement of the classical opioid receptors in vivo. Morphine's inhibitory effect is mediated through the suppression of the hypoxia-induced mitochondrial p38 mitogen-activated protein kinase (MAPK) pathway. Our results suggest that in vitro morphine treatment of LLCs inhibits the hypoxia-induced nuclear translocation of hypoxia-inducible transcription factor 1alpha to reduce vascular endothelial growth factor transcription and secretion, in a manner similar to pharmacological blockade with the p38 MAPK-specific inhibitor, SB203585. These studies indicate that morphine, in addition to its analgesic function, may be exploited for its antiangiogenic potential.

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