Amitriptyline pretreatment preserves the antinociceptive effect of morphine in pertussis toxin-treated rats by lowering CSF excitatory amino acid concentrations and reversing the downregulation of glutamate transporters

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摘要

Abstract

This study was designed to investigate the effect of acute intrathecal (i.t.) injection of amitriptyline (AMI) on the antinociceptive effect of morphine in rats treated with pertussis toxin (PTX). Male Wistar rats were implanted with an i.t. catheter for drug injection and some were implanted with an additional microdialysis probe used for CSF dialysate collection and measurement of excitatory amino acids (EAAs). The expression of glutamate transporters (GTs) in the spinal cord dorsal horn was also measured. A tail-flick test was performed and CSF dialysate was collected as the baseline-B value (day 0) before PTX (1 microg, i.t.) injection and at 4 days after PTX injection, but before drug challenge as the baseline-P value (day 4), and at 30, 60, 90, and 120 min after drug challenge on day 4. The baseline-P tail-flick latencies were significantly lower than the baseline-B values. In PTX-treated rats (day 4), morphine (10 microg, i.t.) did not produce an antinociceptive effect, but this was retained by acute AMI (15 microg, i.t.) pretreatment 30 min before morphine injection. In addition, concentrations of glutamate and aspartate were higher in baseline-P dialysates than in baseline-B dialysates, and the expression of the GTs (GLT-1, GLAST, and EAAC1) was downregulated by PTX treatment. Acute injection of PTX-treated rats with either AMI (15 microg, i.t.) or morphine (10 microg, i.t.) alone had no significant effect on CSF EAA concentrations and GT expression. In contrast, AMI (15 microg, i.t.) pretreatment followed 30 min later by morphine (10 microg, i.t.) injection inhibited the increase in EAA concentrations and reversed the downregulation of all three GTs. Our results show that AMI preserves the antinociceptive effect of morphine in PTX-treated rats. The mechanisms involve suppression of the increase in EAA concentrations in spinal CSF dialysates and reversion of GT expression in PTX-treated rats.