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# Analgesic Effect of Novel 11 β -HSD1 Inhibitor ASP3662 and its Mechanism of Action in a Spinal Nerve Ligation Model of Neuropathic Pain

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Glucocorticoids exert their effects via glucocorticoid receptors (GRs), and the central GR is reportedly involved in the mechanism of neuropathic pain. 11β -hydroxysteroid dehydrogenase 1 (11β -HSD1) is involved in the conversion of inactive glucocorticoids to active glucocorticoids and is expressed not only in peripheral tissues but also in the central nervous system (CNS), such as brain and spinal cord. However, what role—if any—11β -HSD1 plays in pain transmission remains unclear. ASP3662 is a novel 11β -HSD1 inhibitor discovered through our research. Here, we investigated the analgesic effect and mechanism of ASP3662 in a spinal nerve ligation (SNL) model of neuropathic pain in rats. In SNL model rats, the left L5 and L6 spinal nerves were tightly ligated with silk thread. For intrathecal administration, the catheter was inserted between the L5 and L6 vertebrae. In the microdialysis experiment, the spinal cord dialysis probe was passed transversely through the dorsal spinal cord via bilateral holes made through vertebra L1. The mechanical threshold was determined by the von Frey hair test. ASP3662 concentrations in plasma and brain were determined via liquid chromatography-tandem mass spectrometry. One week after spinal nerve ligation, mechanical thresholds of the operated-side hindpaw were clearly lower than those in the sham group (mechanical allodynia). Single oral doses of ASP3662 significantly ameliorated mechanical allodynia, with an $ED_{50}$ value of 0.087 mg/kg at 2 h after administration. Intrathecally administered ASP3662 also alleviated mechanical allodynia. A pharmacokinetics study using SNL model rats revealed CNS penetration by this compound. In a microdialysis experiment, intraperitoneally administered corticosterone, the active glucocorticoid in rodents, significantly increased spinal glutamate concentrations in normal rats. Intraperitoneally administered 11-dehydrocorticosterone (11-DHC), the inactive glucocorticoid in rodents, significantly increased spinal glutamate concentrations in an SNL model but not in normal rats. ASP3662 significantly inhibited this 11-DHC-induced increase in glutamate. ASP3662 is a novel, CNS-penetrable 11β -HSD1 inhibitor which alleviates mechanical allodynia in SNL rats. These results suggest that this compound is a promising candidate for use in treating neuropathic pain. One site of action of ASP3662 is the spinal cord. This compound may block glucocorticoid-induced increases in spinal glutamate concentration in SNL model rats by inhibiting conversion of inactive glucocorticoids into active ones.