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Bi- or multifunctional opioid analgesics

Acute pain typically responds well to treatment with opioids and NSAIDs, whereas neuropathic pain is difficult to treat with only 40-60% of patients achieving pain relief. Currently used treatments, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants and morphine are either ineffective or produce major, limiting side effects. Our goal is to develop opioids with novel bi- or multifunctional activity profiles for treatment of chronic pain with minimal side effects. [Dmt1]DALDA (SS-02), a tetrapeptide with excellent drug-like properties, is a potent mu opioid analgesic and also is a mitochondria-targeted antioxidant. Mitochondrial reactive oxygen species (ROS) play a key role in mechanisms of neuropathic pain and there is evidence that ROS quenchers synergize with opiates in alleviating neuropathic pain. As expected, SS-02 turned out to be more effective than morphine in a rat model of neuropathic pain. Similarly, in a rat model of complex regional pain syndrome (CRPS-1), SS-02 and one of its analogues produced an up to 70-fold more potent and longer-lasting analgesic effect as compared to morphine. A structurally related peptide (SS-20) capable of promoting mitochondrial energetics had a protective effect against the development of chemotherapy-induced peripheral neuropathy in mice. Thus, these compounds are excellent drug candidates for neuropathic pain treatment. In a different approach we developed bifunctional compounds that target two distinct receptors. On the basis of a strong pharmacological rationale compounds were designed that act as agonists at the mu opioid receptor (MOR) and as antagonists at the delta opioid receptor (DOR). Such MOR agonist/DOR antagonists turned out to be potent analgesics in the rat tail flick test with low propensity to produce analgesic tolerance and dependence. Furthermore, bifunctional MOR agonist/NK1 receptor antagonists and opioid agonist/nociceptin antagonists were more potent than morphine in a neuropathic pain model and in one case did not produce respiratory depression.

Recent Publications

1. Schiller P W, Nguyen TM-D, Saray A, Poon A W H, Laferrière A and Coderre T J (2015) The bifunctional μ opioid agonist/antioxidant [Dmt1]DALDA is a superior analgesic in an animal model of complex regional pain syndrome-type 1. ACS Chemical Neuroscience 6:1789-1793.
2. Toyama S, Shimoyama N, Szeto H H, Schiller P W and Shimoyama M (2018) Protective effect of a mitochondria-targeted peptide against the development of chemotherapy-induced peripheral neuropathy in mice. ACS Chemical Neuroscience DOI: 10.1021/acschemneuro.8b00013.
3. Ballet S, Betti C, Novoa A, Tömböly C, Nielsen C U, Helms H C, Lesniak A, Kleczkowska P, Chung N N, Lipkowski A W, Brodin B, Tourwé D and Schiller W (2014) *In vitro* membrane permeation studies and *in vivo* antinociception of glycosylated Dmt1-DALDA analogues. ACS Medicinal Chemistry Letters 5:352-357.
4. Betti C, Mika J, Dyniewicz J, Frankiewicz L, Novoa A, Keresztes A, Kosson P, Van Duppen J, Chung N N, Vandenbroeck J, Lipkowski A W, Schiller P W, Przewlocka B, Tourwé D and Ballet S (2015) Dual alleviation of acute and neuropathic pain by fused opioid agonist-neurokinin 1 antagonist peptidomimetics. ACS Medicinal Chemistry Letters 6:1209-1214.
5. Guillemyn K, Starnowska J, Lagard C, Dyniewicz J, Chung NN, Kosson P, Lipkowski A W, Chevillard L, Megarbane B, Tourwé D, Simonin F, Przewlocka B, Schiller P W and Ballet S (2016) Bifunctional and peptide-based opioid agonist-nociceptin antagonist ligands for dual treatment of acute and neuropathic pain. Journal of Medicinal Chemistry 59:3777-3792.

Biography

Peter W. Schiller is a Medicinal Chemist and Pharmacologist. He is a research Professor in the Department of Pharmacology and Physiology of the University of Montreal and at the Montreal Clinical Research Institute (Canadian Pacific Chair in Pain Research). His research in the opioid field resulted in the discovery of highly receptor-specific agonists and antagonists and of opioids with novel bi-or multifunctional activity profiles. Some of his compounds are widely used as pharmacological tools or are being pursued as analgesic drug candidates. He has published over 400 scientific articles and holds 17 patents. He was elected Fellow of the Royal Society of Canada (Academy of Science) and of the American Association for the Advancement of Science (AAAS). His numerous awards include the Prix Galien of Canada for excellence in pharmaceutical research, a NIH MERIT Award and the Vincent du Vigneaud Award from the American Peptide Society.

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