Targeting endothelin axis to treat pain
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Endothelin participates in a variety of conditions that cause pain. Local injection of ET-1 produces pain which is independent of its vasoactive properties. Pain due to inflammation, nerve injury and cancer has been studied extensively. Most of the studies indicate that ETA receptor antagonists decrease nociception; and some studies indicate that ETB receptor stimulation may be antinociceptive; while others indicate that ETB receptor antagonism may be antinociceptive. However, the idea of ETB receptor stimulation having antinociceptive effect is gaining ground. It was demonstrated that methylation of ETB receptors which results in transcription silencing is present in painful cancerous tissues and not in normal tissues from the same patients. Preclinical studies with ETA receptor antagonists demonstrated potential for reducing pain, and some clinical phase II studies also showed the benefit of using ETA receptor antagonists in reducing cancer pain. In experiments carried out in mice, with deletion of ETA receptors selectively in nociceptive sensory neurons, while preserving expression in non-neuronal cells and the CNS, it was found that ETA receptors are important in the modulation of cancer pain and act independent of ETA receptor function in tumor cells. However, human phase III studies have failed to demonstrate any benefit in reducing pain of cancer patients. It has been found that ETA receptor antagonism predominantly mediates its antinociceptive action through endogenous opiates. Secretion of beta-endorphin and leu-enkephalin is increased by ETA receptor antagonists. ETA receptor antagonists potentiate morphine and oxycodone antinociception in rats and mice; and tolerance to opioid agonists was reversed by treatment with ETA receptor antagonists. Moreover, ETA receptor antagonists enhanced G-protein coupling to opioid receptors and restored morphine analgesia in tolerant animals. This creates the possibility of combination therapies with opioids and ETA receptor antagonists to manage pain in cancer patients with lower doses of opiates and reduced probability of tolerance development.


Endothelin B (ETB) receptor agonist, IRL-1620, has been shown in previous studies, conducted in our lab, to provide significant neuroprotection at both 24 h and 1 week following permanent cerebral ischemia. It is possible that IRL-1620 may be neuroprotective due to angiogenesis and neurogenesis. However, the effect of IRL-1620 on neurovascular remodeling following cerebral ischemia has not been established. The present study was conducted to determine the effect of IRL-1620 [Suc-[Glu9, Ala11, 15]-Endothelin-1 (8–12)] on astrocytes, neurons, and vascular endothelial cells after the induction of cerebral ischemia. Male Sprague-Dawley rats undergoing permanent middle cerebral artery occlusion (MCAO) received three intravenous injections of either vehicle or IRL-1620 (5 μg/kg) at 2, 4, and 6 h post occlusion. Brain tissues of animals euthanized at 24 h or 7 days post occlusion were processed for immunofluorescent labeling of ETB receptors, astrocytes, neurons, and vascular and neuronal growth factors. At 24 h post occlusion, IRL-1620 treatment increased ETB receptor expression and preserved neuronal numbers in the cortex, striatum and subventricular zone of the ischemic rat brain. IRL-1620 also enhanced the number of blood vessels labeled with vascular endothelial growth factor (VEGF) when compared to vehicle treatment. By 1 week following MCAO, VEGF-positive vessels/30 μm brain slice in the IRL-1620 group numbered 11.33 ± 2.13 versus 4.19 ± 0.79 in the vehicle group (P < 0.01). Additionally, animals receiving IRL-1620 displayed an increased number of proliferating cells (P < 0.0001) and cells positively staining for nerve growth factor (P < 0.0001) in the infarcted brain. Results of the present study indicate that IRL-1620, administered on the day of infarct, is neuroprotective and enhances neurovascular remodeling following cerebral ischemia.


Endothelin B receptor agonist, IRL-1620, enhances neurovascular remodeling following cerebral ischemia in rats
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Endothelin receptor A antagonist enhances light-induced damage in the mouse retina
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Exposure to excessive white light induces retinal degeneration or exacerbates the rate of photoreceptor apoptosis in several retinal diseases. In this work we analyzed whether the endothelinergic antagonist Clazosentan (ETRA) could modify the course of light-induced degeneration. We also investigated the possible role of ETA in the transmission of visual stimuli. Male Balb-c mice (5–7 weeks old) were exposed to phototoxic stimuli (1500 lx) for 2 days and 4 days, or exposed to non-phototoxic stimuli (0.3 lx at 2 Hz) for 60 min (n = 3 per group). During the exposure period, animals received saline solution or clazosentan (10 mg/kg/day). 4 days exposed animals were allowed to recover under standard illumination for another 6 days. Mice were then anesthetized;