Adenosine and Histamine Inhibit Ischemic Norepinephrine Release

During myocardial ischemia/reperfusion, lipid peroxidation leads to formation of toxic aldehydes that contribute to ischemic dysfunction. Mitochondrial aldehyde dehydrogenase type 2 (ALDH2) alleviates ischemic heart damage and reperfusion arrhythmias via aldehyde detoxification. This study tested whether reduced norepinephrine release in vitro may be part of the reason for improved function with ALDH2. Incubation of cardiac sympathetic nerve endings under conditions similar to ischemia (high acetaldehyde and hypoxia) caused increases in norepinephrine release. Selective activation of adenosine A1, A3, or histamine H3 receptors markedly inhibited both acetaldehyde and hypoxia-induced norepinephrine release. These effects were correlated with increased ALDH2 activity and were abolished by ALDH2 inhibition. These findings suggest the existence in sympathetic neurons of a protective pathway that could be activated by adenosine and histamine. In addition, this pathway encompasses the activation of ALDH2. Thus, the pharmacological activation of ALDH2 in cardiac sympathetic nerves may have protective effects by alleviating norepinephrine-induced arrhythmias that characterize ischemia/reperfusion.

See article at J Pharmacol Exp Ther 2012, 343:97–105.

Sepantronium Bromide (YM155) Enhances Response of Human B-Cell Non-Hodgkin Lymphoma to Rituximab

In the treatment of B-cell non-Hodgkin lymphoma (B-NHL), rituximab improves long-term survival in combination with conventional chemotherapy. However, because the majority of B-NHL patients eventually relapse, the development of more effective therapies is needed. This study evaluated the antitumor effects of a combination treatment involving sepantronium bromide (YM155), a first-in-class survivin suppressant, and rituximab in B-NHL xenograft mouse models. In DB, WSU-DLCL-2, and Mino xenograft-bearing mice, the combination treatment of YM155 and rituximab induced significant tumor growth inhibition and tumor regression compared with either agent alone. On day 3 after the initiation of treatment, a significant decrease in both 18F-FDG and 18F-FLT tumor uptake from pretreatment levels was observed in combination treatment groups. The Ki-67 proliferation index was significantly decreased on day 3 in the xenograft models treated with combination treatment, suggesting that the combination of YM155 plus rituximab reduced cell proliferation as well as glucose metabolism. These findings demonstrate that YM155 and rituximab combination treatment enhances antitumor activity in B-NHL xenografts, and that 18F-FLT- and 18F-FDG-PET imaging may allow the early functional evaluation of treatment responses in patients with B-NHL.


Modification of Glucocorticoids Dissociates Nuclear Factor-κB Inhibitory Efficacy from Glucocorticoid Response Element-Associated Side Effects

Glucocorticoids are the standard of care for many inflammatory conditions, including lupus, asthma, rheumatoid arthritis, and muscular dystrophy. However, the side-effect profiles of pharmacological glucocorticoids are significant, including muscle atrophy, osteoporosis, spleen atrophy, and mood and sleep disorders. This has led to a search for dissociative steroids—drugs able to retain efficacy without the side effects. This study investigated a glucocorticoid derivative with Δ9,11 modifications as a dissociative steroid. The Δ9,11 analog showed potent inhibition of tumor necrosis factor (TNF) α-induced nuclear factor-κB (NF-κB) signaling in cell reporter assays, and this transrepression activity was blocked by mifepristone (RU486), showing the requirement for the glucocorticoid receptor (GR). The Δ9,11 analog induced nuclear translocation of GR but showed loss of transactivation as assayed by GR-luciferase constructs, as well as mRNA profiles of treated cells. The Δ9,11 analog was tested for efficacy and side effects in two mouse models of muscular dystrophy. Daily oral delivery of Δ9,11 analog showed reduction of muscle inflammation and improvements in multiple muscle function assays, yet no reductions in body weight or spleen size, suggesting loss of key side effects. The data demonstrate that a Δ9,11 analog dissociates the GR-mediated transcriptional activities from anti-inflammatory activities.

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