

Neuropathic Pain and Endocannabinoid-Degradation Blockade

Cannabinoid (CB) receptor agonists alleviate neuropathic hyperalgesia and allodynia but also have undesirable psychoactive effects. An alternative strategy is inhibition of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), the principal enzymes responsible for the degradation of the respective endogenous cannabinoids, anandamide and 2-arachidonylglycerol. Recent results suggest that FAAH and/or MAGL inhibition reduces nociception with minimal behavioral effects. In this issue, Kinsey et al., aim to clarify the role of cannabinoid receptors as mediators of antiallodynic effects of FAAH and MAGL inhibitors in the chronic constriction injury mouse model. The study used two reported FAAH inhibitors and a novel MAGL inhibitor. In the current study, the authors demonstrate that both CB1 and CB2 receptors mediate the antiallodynic responses of FAAH inhibitors, whereas only the CB2 receptor is involved in the antiallodynic effects of an MAGL inhibitor. The study also rules out involvement of opioid receptors in mediating the antiallodynic effects of FAAH inhibitors. The authors conclude that inhibition of FAAH and MAGL reduces neuropathic pain via distinct mechanisms that define viable targets for the development of analgesic therapeutics.

See article at *J Pharmacol Exp Ther* 2009, **330**:902–910.

Ion Channels and the Cardiovascular Response to Propofol

Cardiovascular sensitivity to general anesthetics is highly variable among individuals, but little is known about the genetics of anesthetic responses. Variable responses to anesthetics are also observed in animals. In this issue, Stadnicka et al., describe a study of the role of large conductance calcium and voltage-gated potassium (BK) channels in the cardiovascular response to the general anesthetic propofol. The article extends prior studies by the authors by showing that propofol hyperpolarizes vascular smooth muscle and that this response is accentuated in Dahl salt-sensitive (SS) rats compared with Brown Norway (BN) rats and appears to result from genes carried on a portion of chromosome 13. Propofol modulation of mesenteric arterial smooth muscle cells (MASMC) was evaluated, and the greater hyperpolarization of membrane potential in SS rats was blocked with a BK channel antagonist. The SS rats MASMC also exhibited greater calcium ion sensitivity and a larger whole-cell BK current density. In BN consomic strain rats, with the SS chromosome 13 substitution, the propofol sensitivity and BK channel properties converted to results similar to the background SS strain. The authors conclude that differential BK channel properties and expression underlie cardiovascular responses to propofol. The results support the suggestion that chromosome 13-associated genes are responsible for variable responses to propofol.

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