This study investigated the role of KATP channels in morphine-induced antinociception and hepatic oxidative stress in acute and inflammatory pain. The KATP channel modulators (KATP channel opener, diazoxide 100 mg/kg, p.o, and KATP channel blocker, glibenclamide, 3 mg/kg i.p.) were administered with morphine (80 mg/kg, i.p.). Antinociception was assessed by the tail-flick and formalin tests in rats and measured by the area under the curve values and the maximum percent effect for 3 h. The indices of hepatic oxidative stress: glutathione, glutathione peroxidase, and malondialdehyde were then determined in the liver homogenates obtained from the treated animals. In both tests, glibenclamide antagonized morphine-induced antinociception, whereas diazoxide augmented it in the tail-flick test only. In the formalin test, glibenclamide alone has a significant hyperalgesic effect, whereas diazoxide decreased the number of flinches. Coadministration of glibenclamide with morphine antagonized the hepatotoxic effect of morphine in both animal models. In the tail-flick test, glibenclamide administered alone significantly increased malondialdehyde's level. Coadministration of diazoxide with morphine increased glutathione level in the formalin test. Diazoxide administered alone exacerbated the hepatic oxidative stress in both animal models. These findings suggest a role of KATP channel modulators on morphine-induced antinociception and hepatic oxidative stress. The administration of glibenclamide may prevent morphine-induced hepatotoxicity. The effectiveness of diazoxide in the management of pain is limited due to its deleterious effect on the liver. However, the interaction of the KATP channel modulators with morphine depends on the differential sensitivity to the pain stimulus.