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PD98059 Elevates GSH Levels in Primary Cultured Rat Hepatocytes Independent of MEK Inhibition

Sang K. Kim, Soo Jin, Oh, Jung M. Oh, Kang Y. Yoon,
Hongmei Zhu and Hong-Hee Kim
College of Pharmacy and Research Center for Transgenic Cloned Pigs, Chungnam National University, Daejeon, Korea

The antioxidant activity of flavonoids, directly through scavenging oxidizing species and indirectly through modulating drug-metabolizing enzyme activities, is associated with chemopreventive and chemotherapeutic effects. However, little published information is available concerning the effect of flavonoids on gluthathione (GSH) homeostasis. We previously demonstrated that PD98059, a flavone derivative and selective MEK1 inhibitor, enhanced the insulin-mediated increase in GSH levels (Kim et al, 2004). To determine whether the PD98059-mediated increase in GSH levels was associated with MEK inhibition or the flavone structure of PD98059, primary cultured rat hepatocytes were treated with PD98059, the MEK inhibitor U0126, which is not a flavone derivative, or flavone. PD98059 increased GSH levels in a concentration-dependent manner in hepatocytes cultured in the presence or absence of insulin. In contrast, GSH levels were not affected by U0126 at concentrations sufficient to inhibit insulin-mediated ERK1/2 phosphorylation. Flavone, however, markedly increased GSH levels without inhibition of ERK1/2 phosphorylation. GSH concentration in the culture medium was also increased by PD98059 or flavone, suggesting that the cellular GSH elevation could not be accounted for by the inhibition of GSH efflux into medium. Interestingly, PD98059 and flavone resulted in increased GSH synthesis without elevation of gamma-glutamylcysteine ligase catalytic subunit protein levels or gamma-glutamylcysteine ligase activity. These results provide evidence that PD98059 and flavone produce dramatic changes in GSH homeostasis in hepatocytes, through a mechanism(s) unrelated to MEK inhibition. Moreover, the current study implies that flavonoid-induced chemopreventive and chemotherapeutic effects may be mediated by regulation of redox state through the stimulation of GSH synthesis.

Keyword: D98059, flavone, Glutathione, ERK