Constitutive androstane receptor (CAR) is a nuclear receptor that regulates transcription of various target genes including CYP2B and CYP3A. Transactivation by CAR is regulated by its subcellular localization; however, mechanism that governs the nuclear translocation has not yet been clarified. It has been shown that CYP2B induction by phenobarbital (PB) is attenuated in preneoplastic lesions of rat liver. Unexpectedly, we found that CAR is significantly up-regulated in the liver of rats during chemical carcinogenesis. The present study was designed to elucidate a modulation of CAR function during hepatocarcinogenesis. Male F344 rats and male C3H/He mice were subjected to the modified Solt-Forber protocol. Animals were sacrificed 24 hr after the PB injection. Nuclear and cytosolic protein from rat liver were subjected to Western analysis. Mice were subjected to in vivo transfection using a GFP-CAR expression vector or a PBREM-luciferase reporter construct. Nuclear CAR protein was increased by PB in normal rats; however, no PB-dependent nuclear accumulation of CAR was observed in the rats subjected to the chemical carcinogenesis. Nuclear accumulation of GFP-CAR in response to PB was observed in normal mice, but not in mice subjected to chemical carcinogenesis. Furthermore, PBREM-dependent transactivation in response to PB was attenuated in the liver of mice subjected to chemical carcinogenesis. These observations suggest that impaired nuclear translocation of CAR is involved in the attenuated PB-induction of CYP2B in hepatic tumor of experimental animals.