Vascular endothelial growth factor mRNA levels as a biomarker for short-term N-butyl-N-(4-hydroxybutyl)nitrosamine-induced rat bladder carcinogenesis bioassay

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Generically, carcinogenic effects of chemicals in bladder carcinogenesis are judged by papillary or nodular (PN) hyperplasia induction in rats given N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) for four weeks and the test chemicals for 22-28 weeks. However, up-regulation of vascular endothelial growth factor (VEGF) begins early in rat BBN bladder carcinogenesis. To establish a short term rat bladder carcinogenic bioassay, we analyzed the correlation of VEGF, VEGF mRNA and bladder lesions inductions between 10 and 26 weeks after BBN treatment. Six-week-old male Wistar (slc) rats were given 0.05% BBN for 4, 10 or 26 weeks. To avoid individual rat bias, the bladders were investigated by partial cystectomy at 10 weeks and total cystectomy at 26 weeks. After induction, PN hyperplasia and carcinoma in rats increased with length of BBN treatment and immunohistochemical VEGF expression also increased following carcinogenesis, but immunoreactivity of individual lesions was quite variable. Moreover, induction of PN hyperplasia at 10 weeks BBN treatment was not significantly correlation with that of 26 weeks treatment; then, it was impossible to predict the carcinogenic effect by the induction of PN hyperplasia at 26 weeks BBN treatment by that at 10 weeks BBN treatment. However, VEGF mRNA levels of rat bladders at 10 weeks BBN treatment revealed a strong significant correlation with the incidence of bladder lesions at 26 weeks treatment. Here, we suggest the quantitative VEGF mRNA levels are a good biomarker for short-term BBN induced rat bladder carcinogenesis bioassay.