Metabolism of 4-*n*-Nonylphenol by Non-modified and CYP1A1- and CYP1A2-Transgenic Cell Cultures of Tobacco

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The metabolism of ^{14}C-4-*n*-nonylphenol (^{14}C-4-*n*-NP), as a model for the xenoestrogen nonylphenol, was investigated in three types of tobacco cell suspension cultures: one genetically non-modified culture (NT) and two cultures constitutively expressing human cytochrome P450 CYP1A1 or CYP1A2. With 1 mg l^{-1} of ^{14}C-4-*n*-NP and 24 h of incubation, the xenobiotic was transformed almost completely to glycosides. After glycosidic cleavage, ^{14}C-4-*n*-NP and several primary metabolites of ^{14}C-4-*n*-NP were liberated. Portions of the primary metabolites were 29.3% (NT culture), 34.3% (CYP1A1 culture), and 50.7% of applied ^{14}C (CYP1A2 culture). Thus, the endogenous capacity of the tobacco cells to form primary metabolites of 4-*n*-NP was noticeably higher than that of CYP1A1 or CYP1A2. The results however clearly suggest that 4-*n*-NP is – even though a poor – substrate of CYP1A1 and CYP1A2. In order to examine metabolic profiles of 4-*n*-NP in the NT, CYP1A1 and CYP1A2 cultures, the suspensions were exposed to 10 mg l^{-1} of ^{14}C-4-*n*-NP using a two-liquid-phase system with carrier *n*-hexadecane and 192 h of incubation. Results obtained resembled those of the low concentration study. The oxidative metabolic profiles determined after hydrolytic cleavage using GC-EIMS were similar in the NT, CYP1A1 and CYP1A2 cultures. Main metabolites were side-chain mono-hydroxylated derivatives of 4-*n*-NP with 6′-, 7′- and 8′-OH-4-*n*-NP as prominent metabolites. In addition, olefinic side-chain hydroxy, ring methoxylated, keto and ring hydroxylated derivatives were observed. The lack of differences in metabolic profiles among the CYP1A1, CYP1A2 and NT cultures was referred to the low enzymatic activity of CYP1A1 and CYP1A2 as compared to the higher endogenous oxidative capacity of tobacco, as well as to similar metabolic profiles of 4-*n*-NP produced by CYP1A1 and CYP1A2 and tobacco itself.

Key words: 4-*n*-Nonylphenol, Oxidative Metabolic Profiling, Transgenic Plant Cell Culture