S39-4 Adverse drug reactions and xenobiotic-sensing nuclear receptors

◯Kouichi YOSHINARI[1]

[1]Grad Sch Pharmaceut Sci, Tohoku Univ

Many pharmaceuticals activate xenobiotic-sensing transcription factors, pregnane X receptor (PXR), constitutive androstane receptor (CAR), or Ah receptor, to increase the expression of drug-metabolizing enzymes such as cytochrome P450s. PXR and CAR, belonging to the same nuclear receptor subfamily, enhance the expression of both CYP3A4 and CYP2B6, although PXR and CAR more selectively induce CYP3A4 and CYP2B6 expression, respectively. Because CYP3A4 is involved in the metabolism of a large number of drugs, its induction may cause drug-drug interactions. Thus, CYP3A4 inducibility is widely accessed during the drug development. In contrast, CYP2B6 inducibility is not usually evaluated because of a minor role of CYP2B6 in the drug metabolism. Thus, no clear information will be obtained on the target receptor of drugs (candidates) showing CYP3A4 induction. Recently, the involvement of PXR and CAR in the transcriptional regulation of lipid/carbohydrate metabolism-related genes has also been suggested. In addition, rodent CAR is known to be associated with the hepatotoxicity of acetaminophen and azole antifungal drugs, and with the hepatocyte proliferation and chemical hepatocarcinogenesis. These facts suggest that PXR and CAR could be associated with a wide variety of adverse drug reactions more than expected, and that these receptors may function in a different manner. In this symposium, the new aspects of these receptors in adverse drug reactions will be discussed.