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Omeprazole transactivates human *CYP1A1* and *CYP1A2* expression through the common regulatory region containing multiple xenobiotic-responsive elements

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ABSTRACT

Omeprazole induces human CYP1A1 and CYP1A2 in human hepatoma cells and human liver. Aryl hydrocarbon receptor (AHR) is shown to be involved in this induction. However, its precise molecular mechanism remains unknown because the chemical activates AHR without its direct binding in contrast to typical AHR ligands such as 3-methylcholanthrene (3MC) and β-naphthoflavone (BNF). Human CYP1A1 and CYP1A2 genes are located in a head-to-head orientation sharing about 23 kb 5′-flanking region. Recently, we succeeded to measure *CYP1A1* and *CYP1A2* transcriptional activities simultaneously using dual reporter gene constructs containing the 23 kb sequence. In this study, transient transfection assays have been performed using numbers of single and dual reporter constructs to identify omeprazole-responsive region for CYP1A1 and CYP1A2 induction. Reporter assays with deletion constructs have demonstrated that the omeprazole-induced expression of both *CYP1A1* and *CYP1A2* is mediated via the common regulatory region containing multiple AHR-binding motifs (the nucleotides from −464 to −1829 of human *CYP1A1*), which is identical with the region for BNF and 3MC induction. Interestingly, omeprazole activated the transcription of *CYP1A1* and *CYP1A2* to similar extents while BNF and 3MC preferred *CYP1A1* expression. We have also found that primaquine is an omeprazole-like CYP1A inducer, while lansoprazole and albendazole are 3MC/BNF-like in terms of the CYP1A1/CYP1A2 preference. The present results suggest that omeprazole as well as BNF and 3MC activates both human *CYP1A1* and *CYP1A2* expression through the common regulatory region despite that omeprazole may involve a different cellular signal(s) from BNF and 3MC.

1. Introduction

CYP1A1 and CYP1A2, members of the cytochrome P450 (CYP) gene superfamily, are involved in the detoxification of xenobiotics such as pharmaceutical drugs and environmental pollutants as well as metabolic activation of these compounds. These enzymes are highly inducible. The exposure to certain types of compounds including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 3-methylcholanthrene (3MC), or β-naphthoflavone (BNF) enhances the transcription of *CYP1A1* and

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CYP1A2 to elevate these protein levels. This transactivation is mediated by a receptor-type transcription factor, aryl hydrocarbon receptor (AHR) [1,2]. AHR is normally retained in the cytoplasm and translocates into nucleus upon ligand binding. It then heterodimerizes with AHR nuclear translocator and the heterodimer binds to the *cis*-element called xenobiotic-responsive element (XRE) located in the promoter region of target genes to activate their transcription. The abovementioned chemicals (i.e. TCDD, 3MC, and BNF) causing CYP1A1 and CYP1A2 induction are shown as strong AHR ligands [1,2].

The molecular mechanism of the AHR-mediated activation of *CYP1A* genes have been extensively studied on *CYP1A1* and several XREs are identified in the 5′-flanking region of human as well as rodent CYP1A1 genes. In contrast, the molecular mechanism of CYP1A2 induction has been unclear. Because Cyp1a2 induction by TCDD or 3MC is deficient in Ahr-null mice, AHR is believed to be involved in the CYP1A2 induction. However, no XRE sequence has been identified in the CYP1A2 promoter sequence in previous reports.

Human CYP1A1 and CYP1A2 genes are located on chromosome 15 in a head-to-head orientation and share about 23 kb 5′-flanking region. This has raised the possibility that these genes share a common regulatory element(s). To test this hypothesis, we have recently prepared dual reporter gene constructs containing the 23 kb sequence, with which we are able to measure *CYP1A1* and *CYP1A2* transcriptional activities simultaneously as different reporters, luciferase (Luc) and secreted alkaline phosphatase (SEAP), respectively [3]. The transient transfection assays with the various dual reporter constructs have demonstrated that the region from −464 to −1829 of human *CYP1A1*, which contains five XREs, is necessary for 3MC- and BNF-induced expression of not only *CYP1A1* but *CYP1A2* as well [3].

Omeprazole, a proton pump inhibitor with a benzimidazole structure, has been shown to induce CYP1A1 and CYP1A2 in human hepatoma cell lines and human liver in vitro and in vivo [4–8]. The molecular mechanism of this induction, however, remains obscure. In contrast to TCDD, 3MC, and BNF, omeprazole is shown to activate AHR without its direct binding [9–13] and this activation seems to require an additional cellular factor(s) [12,14–16]. To understand the mechanism for the omeprazole induction of human CYP1A1 and CYP1A2, here we have sought to identify an omeprazole-responsive promoter region by transient transfection assays using the dual reporter constructs.

2. Materials and methods

2.1. Materials

Omeprazole, lansoprazole, albendazole, BNF, 3MC, and primaquine were purchased from Sigma–Aldrich (St. Louis, MO) and their chemical structures are shown in Fig. 1. Dimethyl sulfoxide (DMSO) was from Wako Pure Chemicals (Osaka, Japan). HepG2 cells were obtained from Riken Bioresource Center (Tsukuba, Japan).

2.2. Reporter gene assays

The single and dual reporter plasmids for human *CYP1A1* and/or *CYP1A2* were reported previously [3]. HepG2 cells were

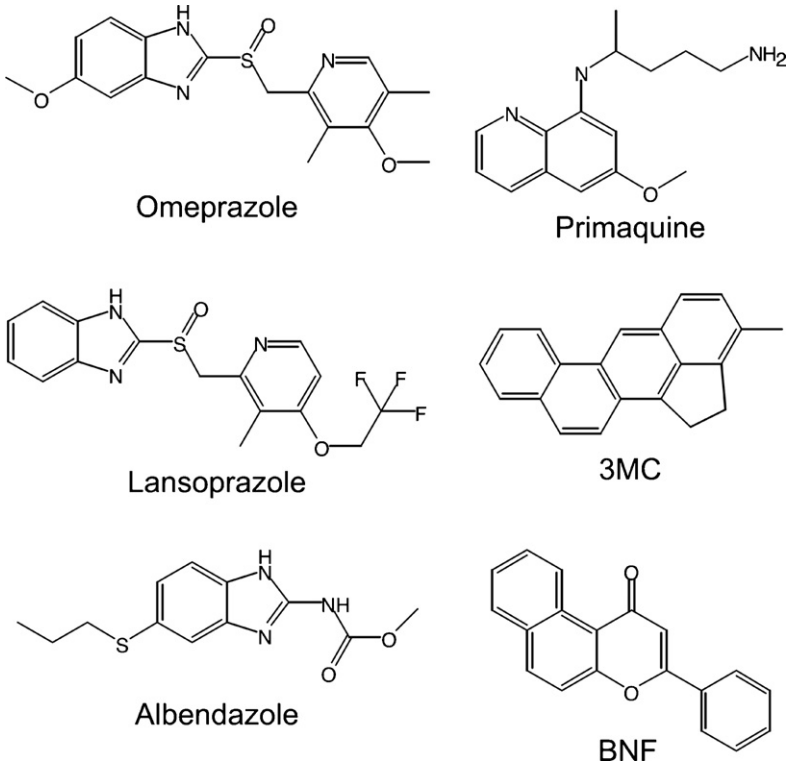

Fig. 1 – Chemical structures of the compounds used in this study.

cultured in Dulbecco's modified Eagles medium (Sigma–Aldrich) supplemented with MEM nonessential amino acids (Invitrogen, Carlsbad, CA), antobiotic–antimycotic (Invitrogen), and 10% fetal bovine serum (Sigma–Aldrich). Transient transfection and measurement of reporter activities were performed as described previously [3]. Briefly, HepG2 cells (1.0×10^4 cells per well) were seeded in 48-well Plates 12 h before transfection, and reporter plasmids (0.15 μg/well) were transfected using FuGene6 (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions. The cells were then treated with various compounds (dissolved in DMSO) or vehicle for 40 h with a final concentration of DMSO at 0.1%. To normalize the transfection efficiency pSV-β-gal (Clontech, Mountain View, CA) or pRL-SV40 (Promega, Madison, WI) was cotransfected.

2.3. Statistical analysis

One-way analysis of variance followed by Dunnett's post hoc test was carried out using Prism software version 4 (GraphPad Software Inc., San Diego, CA).

3. Results

3.1. Selectivity of omeprazole for the CYP1A1 and CYP1A2 transactivation

In this study, we have employed human hepatoma HepG2 cells to investigate the omeprazole-dependent transactivation of human CYP1A1 and CYP1A2 genes because various CYP1A-inducing compounds including omeprazole increased both CYP1A1 and CYP1A2 mRNA levels in the cells [3,8,17–19] and the expression of AHR and AHR nuclear translocator was reported in the cell line [17,19]. The full-length dual reporter construct, pd-1A1/1A2, containing the nucleotides from −23,411 to +1039 of human *CYP1A1* (corresponding to those from −24,354 to +90 of human *CYP1A2*), was transfected into HepG2 cells, and Luc (for *CYP1A1* transcription) and SEAP (for *CYP1A2* transcription) activities were determined to compare the ratio of these reporter activities. As shown in Fig. 2, all compounds including omeprazole increased SEAP activities to similar extents, while omeprazole and primaquine poorly enhanced Luc activities as compared to other compounds. Interestingly, lansoprazole and albendazole, which have a benzimidazole moiety as omeprazole (Fig. 1) [5,6,18], showed a preference similar to that of BNF and 3MC rather than omeprazole. An anti-malaria drug primaquine [18,20] increased both Luc and SEAP activities equally as omeprazole.

3.2. Omeprazole-responsive region of human CYP1A1 and CYP1A2 assessed with single reporter constructs

To identify an omeprazole-responsive region, a series of *CYP1A1* reporter constructs were transiently transfected into HepG2 cells and SEAP activities were determined after omeprazole treatment (Fig. 3). When p1A1-12188 was transfected, SEAP activities were increased 10-fold by omeprazole treatment. p1A1-8653 showed a similar response. However, the omeprazole-dependent increase in the SEAP activity was slightly enhanced when the nucleotides from −12,188 to −6445 of human *CYP1A1* were deleted. The deletion of nucleotides up to −887, leaving a single XRE, reduced the response by 70% from p1A1-5058. As expected, both p1A1-12188D and p1A1-8653D containing no XRE, barely responded to omeprazole treatment. These results were similar to those with BNF and 3MC [3].

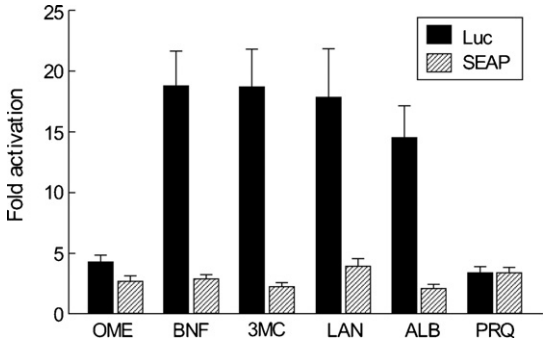

Fig. 2 – Transcriptional activation of human *CYP1A1* and *CYP1A2* by various compounds. HepG2 cells were transiently transfected with pd-1A1/1A2 and pRL-SV40, and treated with omeprazole (25 μM; OME), BNF (10 μM), 3MC (1 μM), lansoprazole (25 μM; LAN), albendazole (5 μM; ALB), primaquine (25 μM; PRQ), or vehicle (DMSO at a final concentration of 0.1%) for 40 h. Then, reporter activities were determined. Luc and SEAP activities were normalized with *Renilla* Luc activities, and are expressed as the ratio to those in vehicle-treated cells. Data are the mean ± S.E.M. of three-independent experiments performed in triplicate.

Next, a series of *CYP1A2* reporter constructs were utilized (Fig. 4). When p1A2-22430 containing 11 out of 12 XREs was used, omeprazole treatment increased the reporter activity sixfold. However, the omeprazole-dependent increase of reporter activity was completely lost by the deletion of the nucleotides from −22,430 to −14,664 of human *CYP1A2*. Further deletion to −3203 had little effect on the drug response. In contrast, the deletion of the nucleotides from −18,237 to −5221 with five XREs reduced omeprazole response minimally compared with p1A2-22430. These results were comparable to those with BNF and 3MC [3].

3.3. Omeprazole-responsive region of human CYP1A1 and CYP1A2 assessed with dual reporter constructs

To further explore the omeprazole-responsive region, we next employed a series of dual reporter constructs. As shown in Fig. 5, omeprazole increased Luc and SEAP activities 4- to 5-fold and 2.5- to 3-fold, respectively, when pd-1A1/1A2 was transfected into HepG2 cells. The deletion of nucleotide from −18,096 to −4621 of *CYP1A1* (−18,704 to −5221 of *CYP1A2*) had little effect on the omeprazole activation of the reporter genes. However, further deletion to −887 (−22,430 of *CYP1A2*), leaving two XREs, decreased the fold activation of Luc and SEAP activities by 50 and 30%, respectively. Moreover, the construct lacking the nucleotides from −464 to −18,096 of *CYP1A1* (−22,852 to −5221 of *CYP1A2*) did not respond to omeprazole

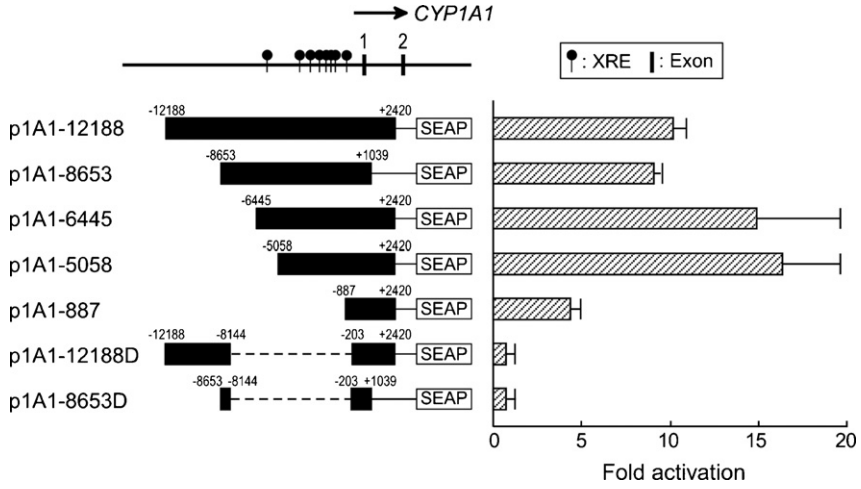

Fig. 3 – Identification of an omeprazole-responsive region of human *CYP1A1* using single reporter constructs. HepG2 cells were transiently transfected with a series of *CYP1A1* reporter constructs (shown on the left) and pSV-β-gal. The cells were treated with 25 μM of omeprazole or vehicle (DMSO at a final concentration of 0.1%) for 40 h, and then SEAP and β-galactosidase activities were determined. SEAP activities were normalized with β-galactosidase activities, and are expressed as the ratio to those in vehicle-treated cells (right panel). Data are the mean ± S.E.M. of three-independent experiments performed in triplicate. Numbers in the left panel indicate the positions from the transcription initiation site of CYP1A1 gene. A schematic structure of human CYP1A1 gene is shown on the top.

treatment. On the other hand, the deletion of the nucleotides from −21,992 to −18,909 of *CYP1A1* (−4412 to −1329 of *CYP1A2*) increased the omeprazole induction of Luc and SEAP activities 2- and 1.4-fold, respectively. Further deletion to −1829 of *CYP1A1* (−21,492 of *CYP1A2*) had no effect on the drug-dependent activation of Luc activities but increased that of SEAP. The construct lacking the nucleotides from −21,992 to −1829 (−21,492 to −1329 of *CYP1A2*) was most strongly activated. When all the XREs were removed, omeprazole treatment increased neither Luc nor SEAP activities as expected. These results were similar to those obtained with BNF and 3MC as in the case of single reporter constructs [3].

3.4. *Multiple XREs are responsible for omeprazole induction*

Based on the results obtained with the single and dual reporter constructs, the region from −1829 to −464 of *CYP1A1* (−22,852 to −21,492 of *CYP1A2*) may be the omeprazole-responsive region for the transcriptional activation of both CYP1A1 and

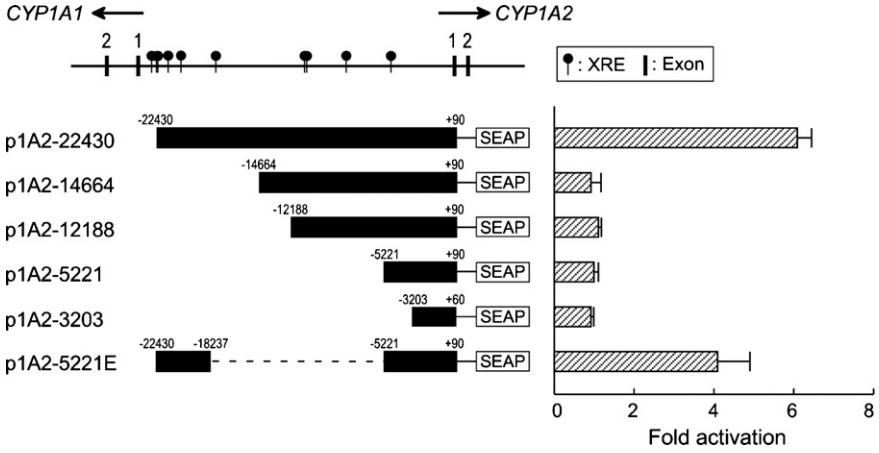

Fig. 4 – Identification of an omeprazole-responsive region of human *CYP1A2* using single reporter constructs. HepG2 cells were transiently transfected with a series of *CYP1A2* reporter constructs (shown on the left) and pSV-β-gal. The cells were treated with 25 μM of omeprazole or vehicle (DMSO at a final concentration of 0.1%) for 40 h, and then SEAP and β-galactosidase activities were determined. SEAP activities were normalized with β-galactosidase activities, and are expressed as the ratio to those in vehicle-treated cells (right panel). Data are the mean ± S.E.M. of three-independent experiments performed in triplicate. Numbers in the left panel indicate the positions from the transcription initiation site of CYP1A2 gene. A schematic structure of human CYP1A1 and CYP1A2 genes is shown on the top.

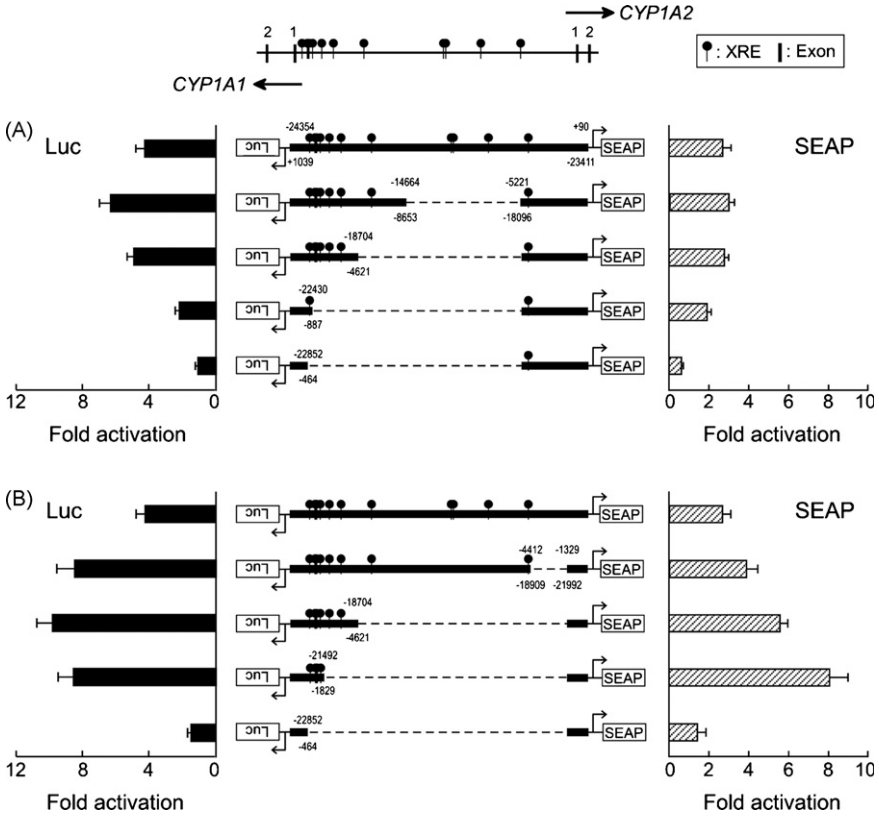

Fig. 5 – Identification of an omeprazole-responsive region of human *CYP1A1* and *CYP1A2* using dual reporter constructs. HepG2 cells were transiently transfected with a series of dual reporter constructs (shown in the center) and pRL-SV40. The cells were treated with 25 μM of omeprazole or vehicle (DMSO at a final concentration of 0.1%) for 40 h, and then reporter activities were determined. Luc and SEAP activities were normalized with *Renilla* Luc activities, and are expressed as the ratio to those in vehicle-treated cells (left and right panels, respectively). The sets of constructs shown in A and B were independently investigated. Data are the mean ± S.E.M. of three-independent experiments performed in triplicate. The numbers below and above the constructs indicate the positions from the transcription initiation site of CYP1A1 and CYP1A2 genes, respectively. A schematic structure of human CYP1A1 and CYP1A2 genes is shown on the top.

CYP1A2 genes. Because this region contains five XREs (named XRE1 to XRE5 from the *CYP1A1* transcription start site), the reporter constructs lacking one of five XREs were prepared and the contribution of each XRE to omeprazole induction was investigated (Fig. 6). For the *CYP1A1* transcription, the deletion of XRE1 or XRE3 significantly reduced the drug response. The deletion of other XREs also tended to reduce the response although there was no statistical significance. For the *CYP1A2* transcription, all the deletion constructs showed slightly reduced omeprazole responses with the deletion of XRE1, XRE3, or XRE5 being statistically significant.

4. Discussion

Omeprazole increases CYP1A1 and CYP1A2 levels in human hepatocytes in vitro and in vivo. Although AHR is involved in this induction, its molecular mechanism is believed to be different from that for TCDD, 3MC, and BNF. Recently, we have prepared the dual reporter gene constructs, which enable us to determine transcriptional activities of human *CYP1A1* and *CYP1A2* simultaneously as Luc and SEAP activities, respectively. In the present study, we have employed these constructs to investigate transcriptional activation of those genes by omeprazole in HepG2 cells. Reporter assays with various deletion constructs demonstrated that the omeprazole-induced activation was mediated via the region (−464 to −1829 of *CYP1A1*/−22,852 to −21,492 of *CYP1A2*) containing multiple XREs, which was demonstrated to be necessary for the BNF- and 3MC-mediated activation of both genes in our previous study [3]. Omeprazole activated both CYP1A1 and CYP1A2 genes to a similar extent while BNF and 3MC activated CYP1A1 gene expression preferentially, when the full-length dual reporter construct was used. This difference remains to be investigated in future studies. In addition, the mechanism by which omeprazole activates AHR remains elusive: Omeprazole has been reported to activate AHR without direct binding [9–13], which may involve a protein kinase(s) [12,14–16]. Nevertheless, our present results strongly suggest that omeprazole activates both human *CYP1A1* and *CYP1A2* transcription through the common regulatory region as typical AHR ligands.

In our previous study, the nucleotides from −18,909 to −21,992 of *CYP1A1* was identified as a negative regulatory

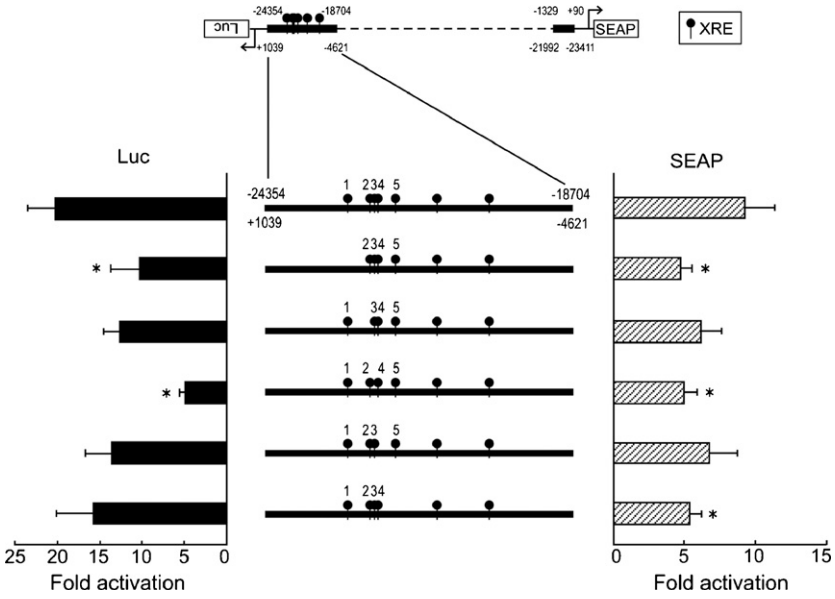

Fig. 6 – Role of XREs in omeprazole-induced expression of human *CYP1A1* and *CYP1A2*. HepG2 cells were transiently transfected with a wild-type or an XRE-deleted dual reporter constructs (shown in the center), and pRL-SV40. The cells were treated with 25 μM of omeprazole or vehicle (DMSO at a final concentration of 0.1%) for 40 h, and then reporter activities were determined. Luc (left) and SEAP (right) activities were normalized with *Renilla* Luc activities, and are expressed as a ratio to those in vehicle-treated cells. Data are the mean ± S.E.M. of three-independent experiments performed in triplicate. An asterisk represents statistically significant difference ($P < 0.05$ assessed by one-way analysis of variance followed by Dunnett's post hoc test) against the wild-type construct (shown on the top). A schematic structure of the wild-type reporter construct is shown on the top. The numbers below and above the constructs indicate the positions from the transcription initiation site of CYP1A1 and CYP1A2 genes, respectively.

region for the BNF- and MC-dependent transcription of CYP1A1 and CYP1A2 genes [3]. In this study, this region was also shown to negatively regulate the omeprazole-dependent activation of these genes. Although a transfactor(s) for the negative regulation is unknown at present, these results further support the idea that the omeprazole-induced transcription of CYP1A1 and CYP1A2 genes is mediated through the identical promoter regions for the BNF- and 3MC-induced transcription.

The positive regulatory region (−464 to −1829 of *CYP1A1*/−22,852 to −21,492 of *CYP1A2*) contains five XREs. We thus investigated the contribution of each XRE to the omeprazole-induced transcription of *CYP1A1* and *CYP1A2* by use of deletion constructs. Interestingly, the results were slightly different between these two genes. For the *CYP1A1* transcription, the deletion of XRE3 (the 3rd XRE from the *CYP1A1* transcription start site) most drastically reduced the omeprazole-induced activation (by 76%) and the others showed 22–49% reduction. On the other hand, each XRE showed similar consequences in the omeprazole-induced *CYP1A2* transcription. The deletion of a single XRE reduced the response by 27–49%. These results are similar to those with BNF [3]. Therefore, the present results suggest that the AHR activated by omeprazole and the one activated by BNF recognize the same XREs located in the positive regulatory region (−464 to −1829 of *CYP1A1*/−22,852 to −21,492 of *CYP1A2*). These XREs work cooperatively with a different contribution in a gene-dependent manner.

In addition to omeprazole, we tested lansoprazole and albendazole, other benzimidazole-containing compounds, for their abilities to activate the dual reporter construct. The former compound is clinically used as a proton pump inhibitor as omeprazole. All these compounds have been reported to induce both CYP1A1 and CYP1A2 in human hepatocytes and in HepG2 cells [5,6,8,18]. In addition, lansoprazole, with a similar chemical structure with omeprazole, was shown not to bind to human AHR [5] as omeprazole. Despite that, these chemicals behaved similarly with BNF and 3MC rather than omeprazole in terms of their preference for the *CYP1A1* transcription. Albendazole was shown to increase CYP1A1 mRNA levels more efficiently than those of CYP1A2 in HepG2 cells [18], which is consistent with our results. The reason for the distinct transcriptional preferences for *CYP1A1* and *CYP1A2* among omeprazole and these compounds remains obscure at present.

Omeprazole sulfide, a degradation product of omeprazole, has been reported as an antagonist for AHR in HepG2 cells but it acts as an agonist for AHR in human hepatocytes owing to the CYP3A4-mediated transformation of the sulfide to omeprazole [16]. Lansoprazole is also converted to its sulfide nonenzymatically [21]. Because HepG2 cells have little CYP activities, CYP-mediated metabolism of the inducers is unlikely to occur in this cell line. Although it is unknown whether lansoprazole sulfide and/or albendazole behaves as an antagonist for AHR in HepG2 cells, it could be possible that only omeprazole sulfide has such an antagonistic activity among the benzimidazole derivatives used in this study and effectively suppresses *CYP1A1* expression in HepG2 cells. This possibility remains to be investigated in future studies.

In contrast to lansoprazole and albendazole, primaquine activated *CYP1A1* and *CYP1A2* expression to similar extents as omeprazole. Consistently, this antimalarial drug has been reported to increase both CYP1A1 and CYP1A2 mRNA levels in HepG2 cells, with relatively low selectivity for CYP1A1 and CYP1A2 compared to albendazole [18]. In addition, the compound did not to bind to human AHR [20]. These results suggest that primaquine is an omeprazole-like inducer of human CYP1A1 and CYP1A2.

In conclusion, our present results clearly indicate that omeprazole activates both human CYP1A1 and CYP1A2 gene expression through the common regulatory region containing multiple XREs, which is the same region for BNF and 3MC induction, despite that the omeprazole-dependent expression of these genes may involve a different intracellular signal(s) from those for the BNF/3MC-induced ones.

Acknowledgments

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