25Th JSSX Annual Meeting in Tokyo

Expression and Genome Analyses of Drug Transporters and Their Clinical Applications

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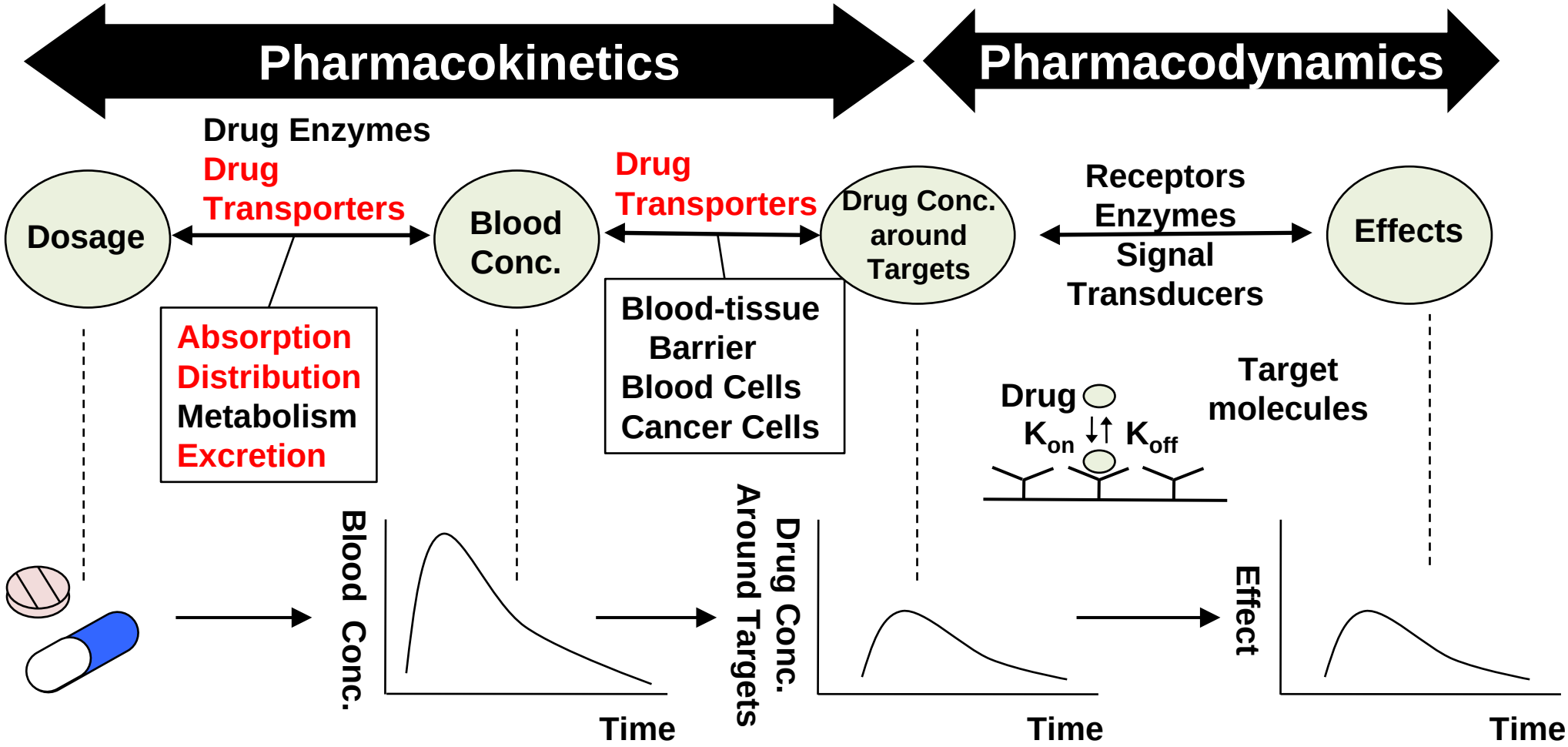
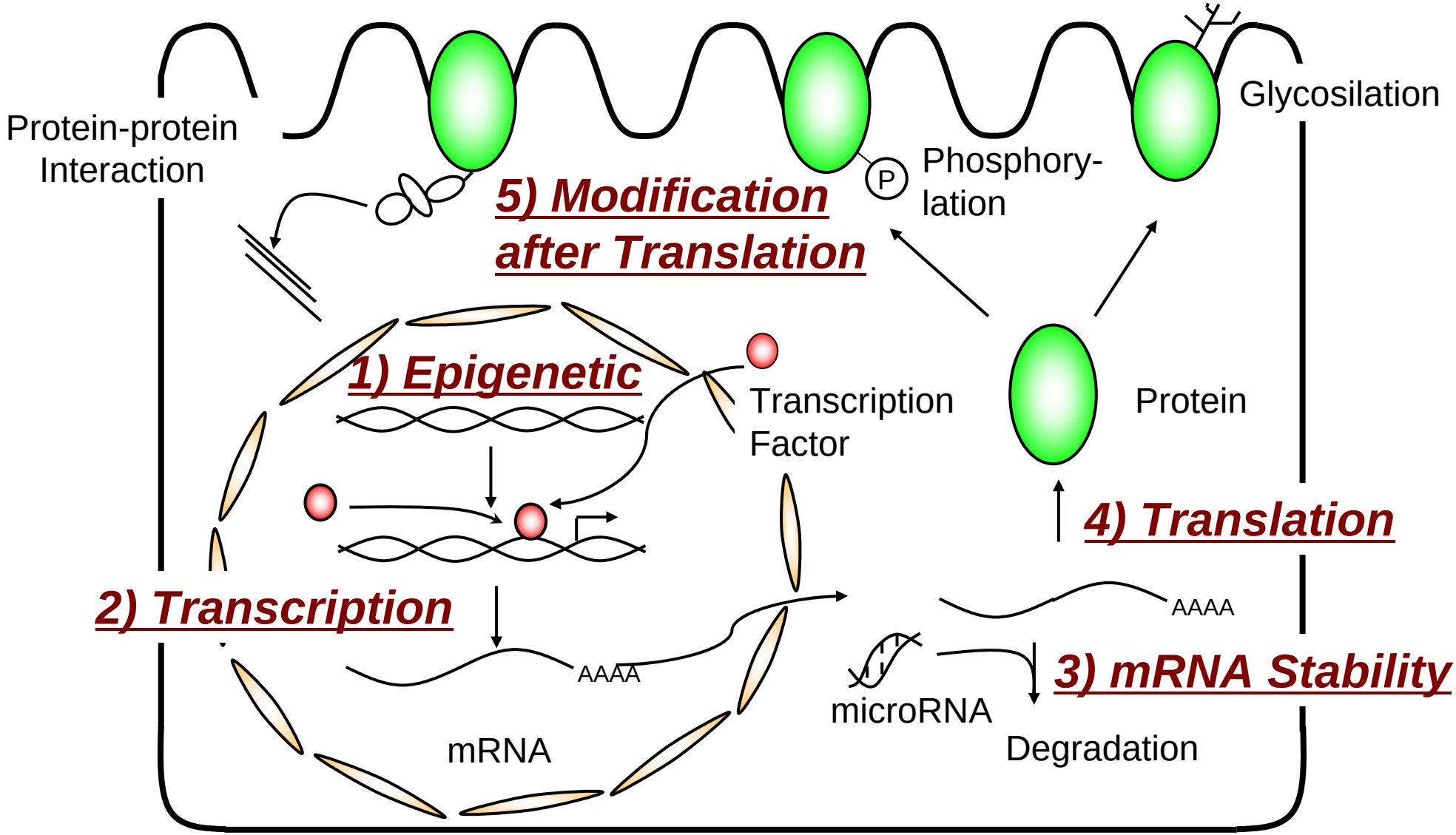
PK/PD and Drug Transporters



Qualitative and quantative alteration of drug transporters can affect the PK/PD, and sometimes the drug effects. Quantitative alteration of drug transporters are directly related to the expression of drug transporters.

Potential Regulatory Mechanisms of Drug Transporters' Expression



1. **Transcriptional Mechanisms of Drug Transporters**

2. **Expression and Genome Analyses of Hepatic and Renal Drug Transporters**

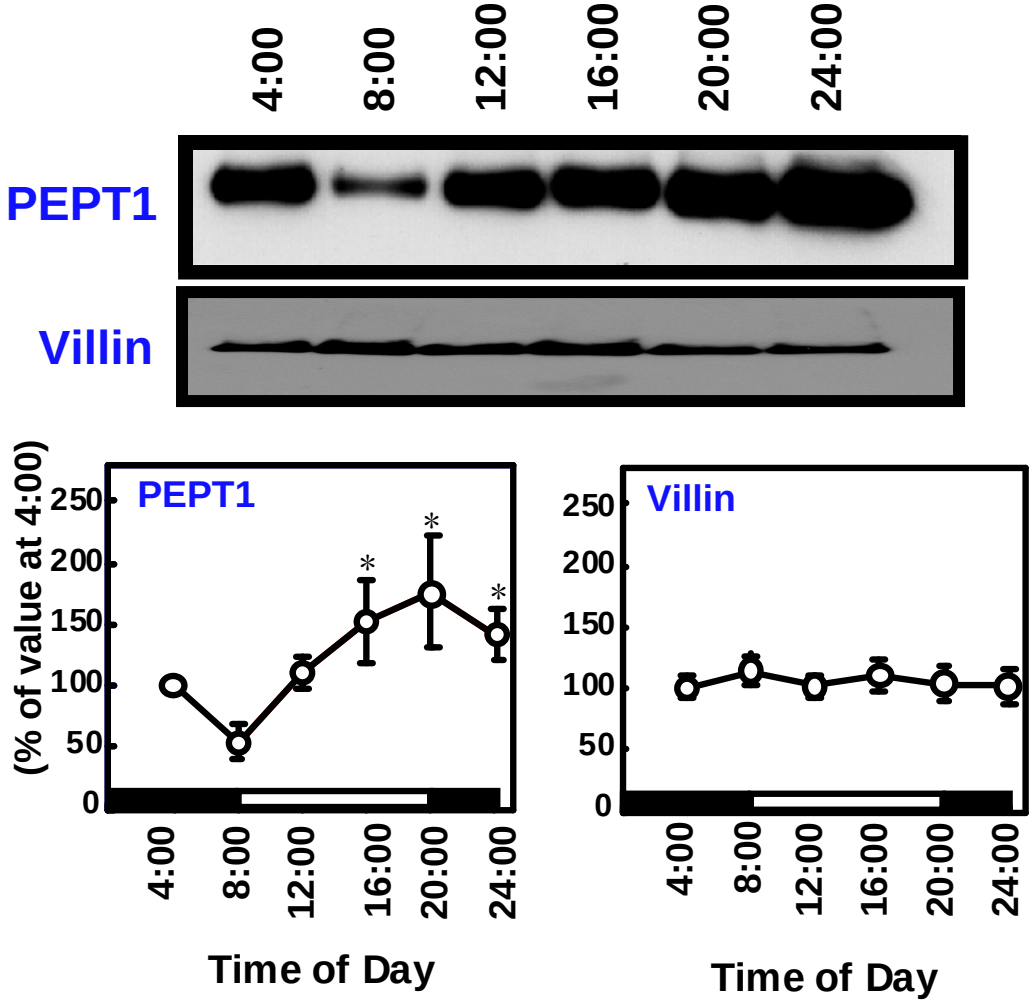
Gene Regulation of Drug Transporters

Gene	Tissue	*Cis*-element	Transcription Factor	Regulation	Ref.
PEPT1	Intestine	GC Box	Sp1		AJP, 2005
	Intestine		Cdx2	Intestinal Expression	BCP, 2006
	Intestine		PPARα	Fasting	AJP, 2007
	Intestine	DBP-binding site	DBP	Diurnal Rhythm	AJP, 2008
OCT1	Liver	E-box	USF1/2		AJP, 2008
	Liver			DNA Methylation	AJP, 2008
OCT2	Kidney	E-box	USF1		JPET, 2007
	Kidney			DNA Methylation	AJP, 2008
	Kidney	ARE	AR	Testosterone	Pharm. Res., 2006
OAT1	Kidney	IR-8	HNF-4α		AJP, 2007
OAT3	Kidney	CRE	CREB1/ATF1		JPET, 2006
	Kidney			Cholestasis	AJP, 2008
MATE1	Kidney	GC Box	Sp1		AJP, 2007
MRP4	Liver			HCV, LC	DMPK. 2010

Review Terada and Inui: Gene expression and regulation of drug transporters in the intestine and kidney. Biochem. Pharmacol., 73, 440-449 (2007)

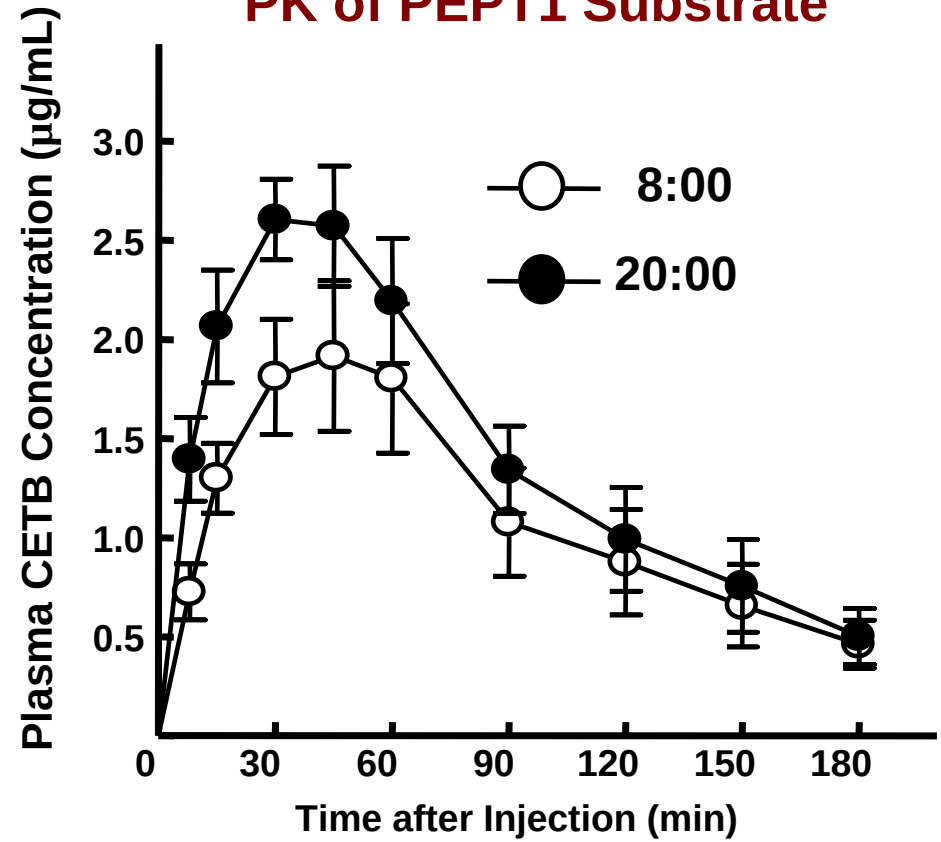
Diurnal Rhythm of Intestinal PEPT1

PEPT1 Protein Expression



Pan et al., Am J Physiol., 283, G57-G64 (2002)

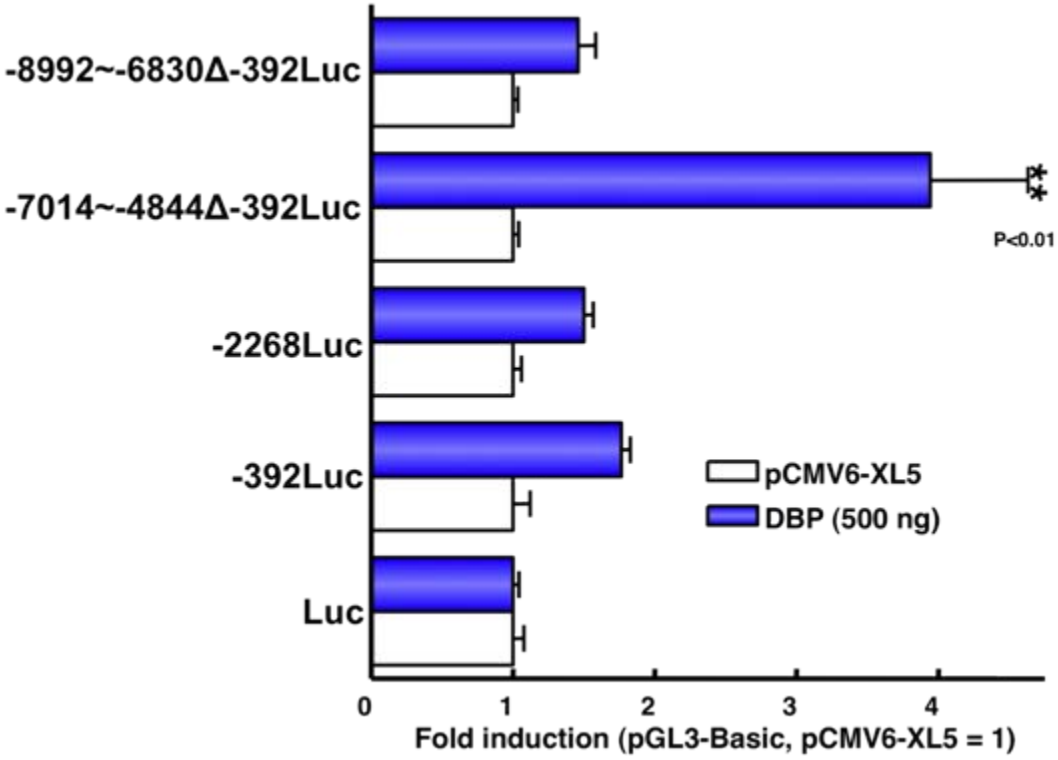
Effect of Diurnal Rhythm on PK of PEPT1 Substrate



Pan et al., JPET, 307, 626-632 (2003)

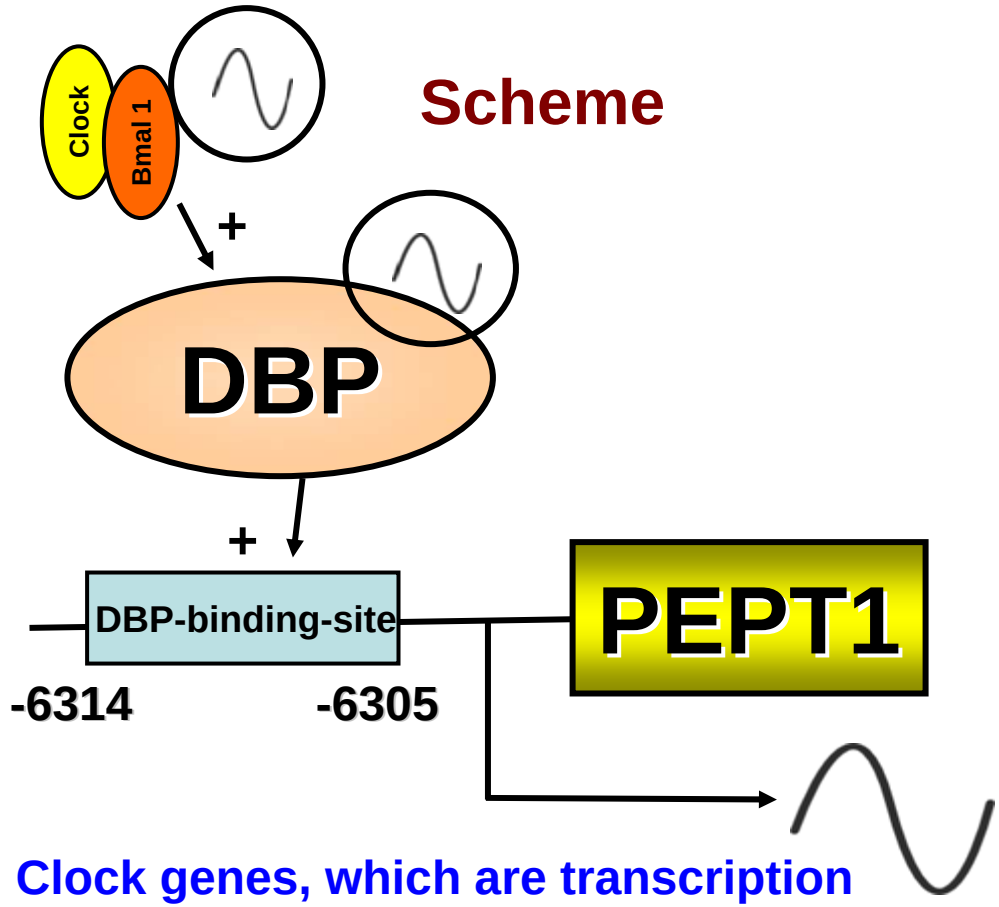
Molecular Mechanisms of Diurnal Rhythm of PEPT1

Luciferase Assay



Saito et al., Am J Physiol, 295, G395-G402 (2008)

Scheme



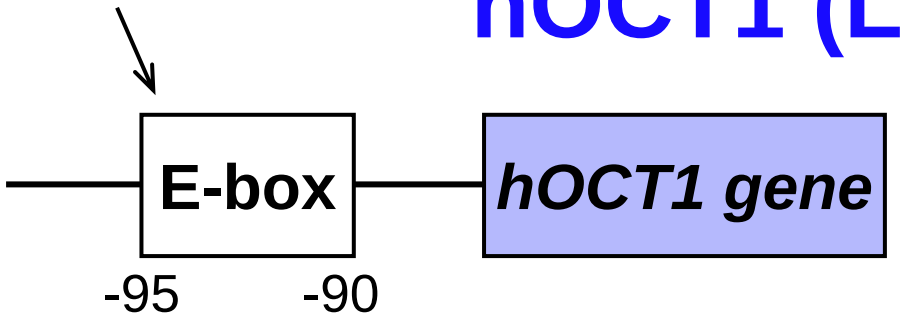
Clock genes, which are transcription factors, can regulate the diurnal rhythm of DBP, another transcription factor. The DBP then regulate the diurnal rhythm of intestinal PEPT1 gene expression.

Tissue Specific Expression of OCT1 & OCT2

Transcription Factor

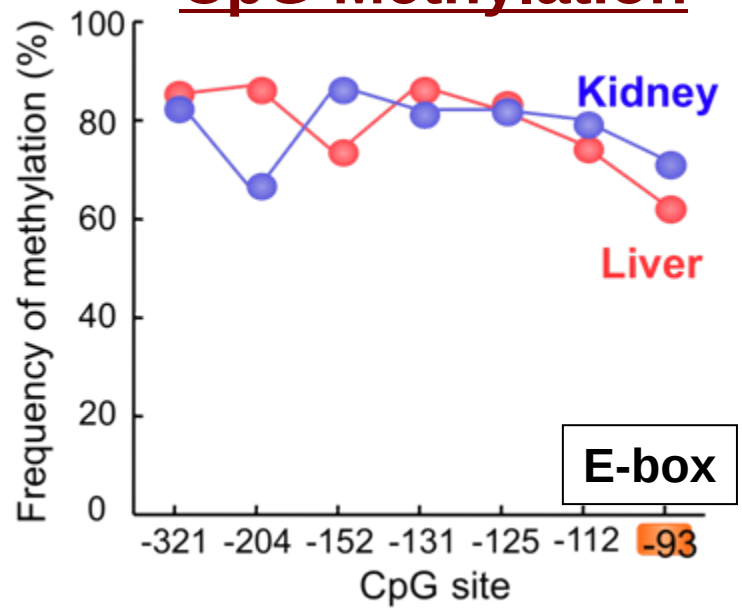
USF1/USF2

hOCT1 (Liver)



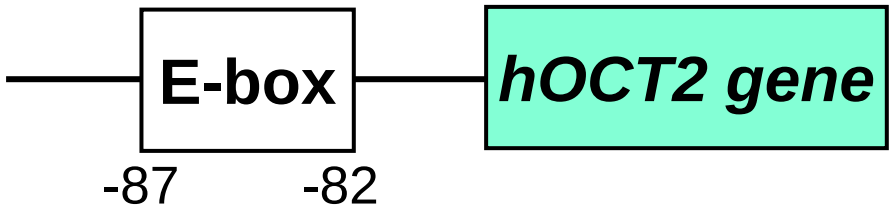
Kajiwara et al., AJP, 295, G1211-G1216 (2008)

CpG Methylation

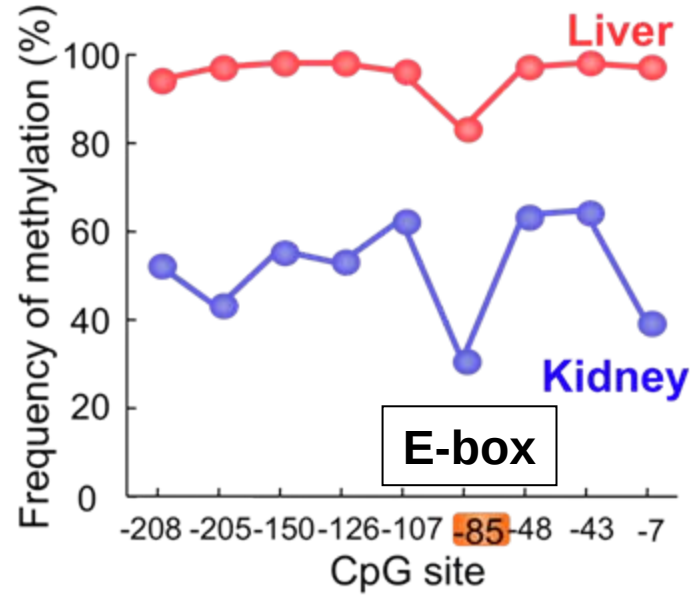


USF1

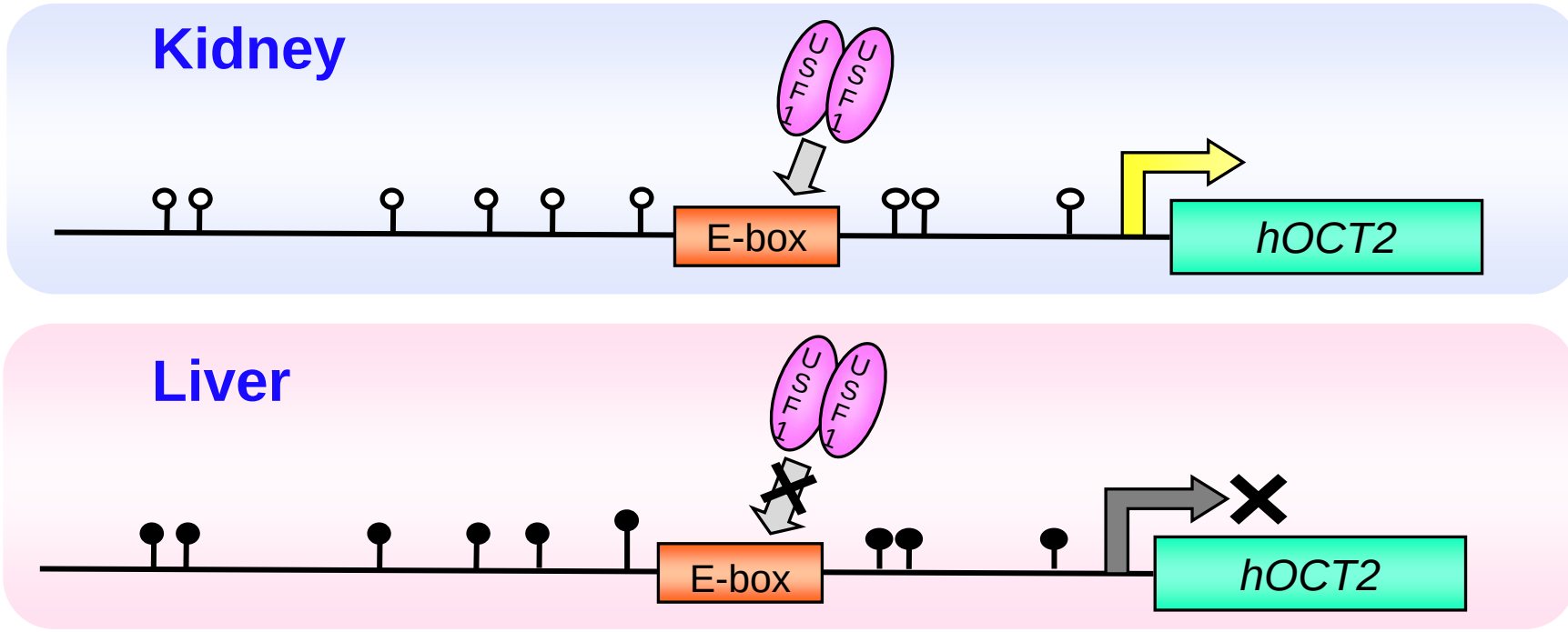
hOCT2 (Kidney)



Asaka et al., JPET, 321, 684-689 (2007)



Tissue Specific Expression OCT2



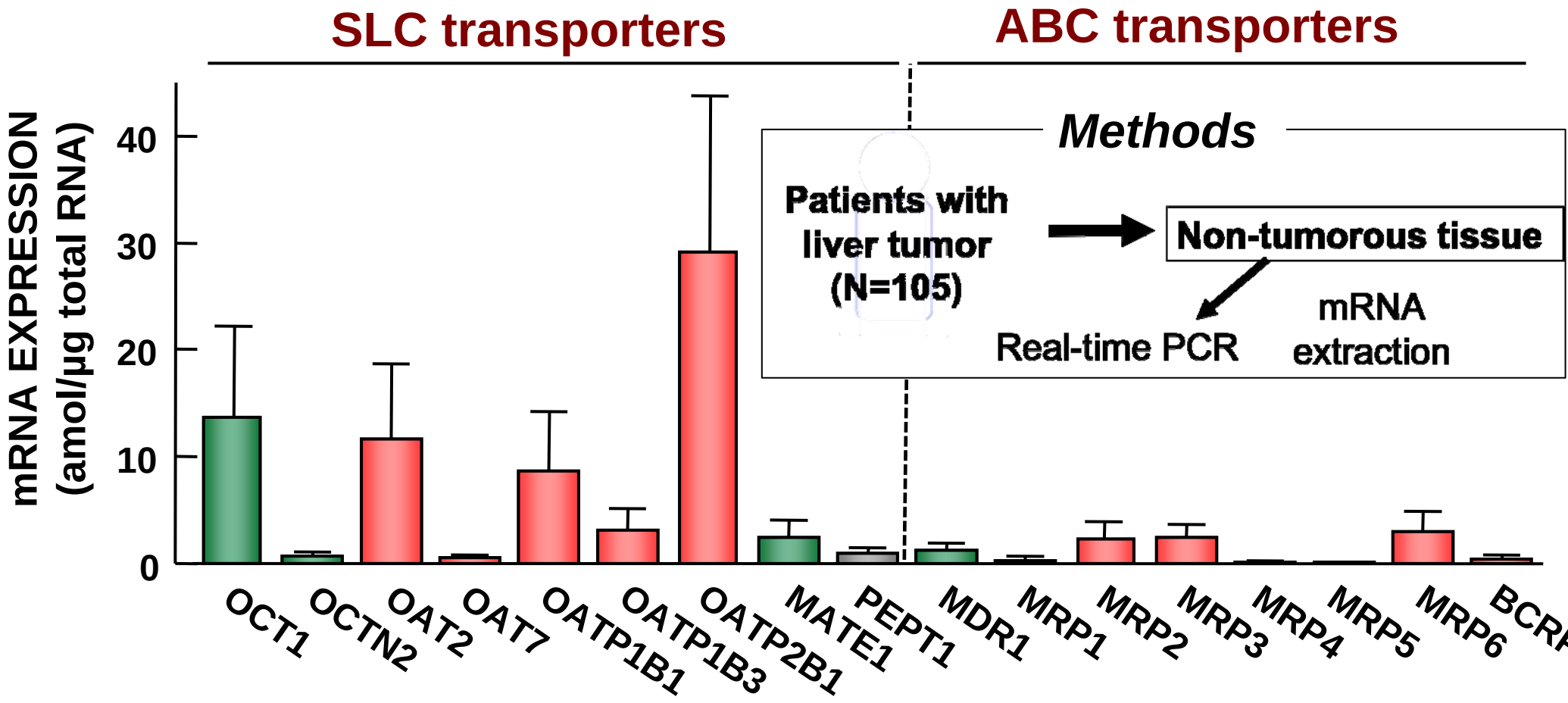
Kidney-specific expression of human OCT2 is regulated by DNA methylation of the proximal promoter region, interfering with the transactivation by USF1.

Aoki et al., Am. J. Physiol., 295, F165-F170 (2008)

1. Transcriptional Mechanisms of Drug Transporters

2. **Expression and Genome Analyses of Hepatic and Renal Drug Transporters**

Expression Profiles of Drug Transporters in the Human Liver



Mean ± S.D. (N = 105)

OCT2, OCT3, OCTN1, OAT1, OAT3, OAT4, MATE2-K and PEPT2:
Mean mRNA levels were lower than 0.5 amol/μg total RNA.

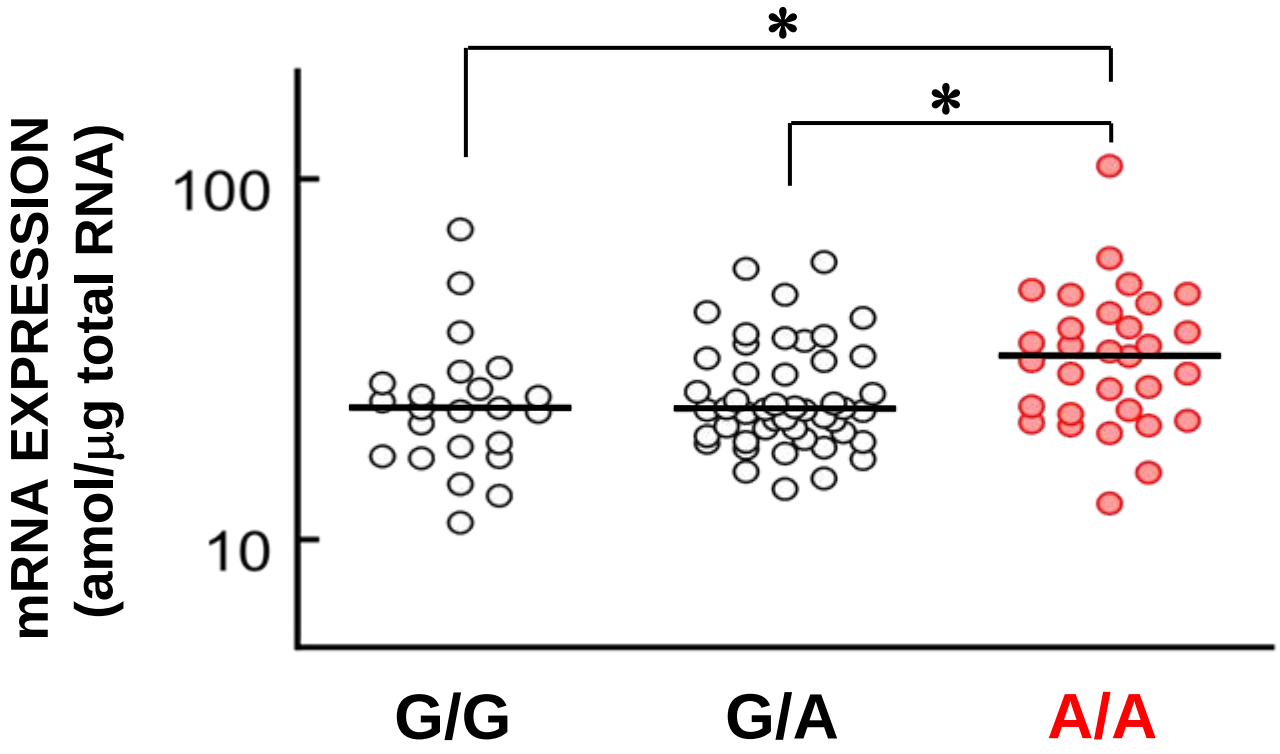
Ogasawara et al., DMPK, 25, 190-199 (2010)

rSNPs of Drug Transporters

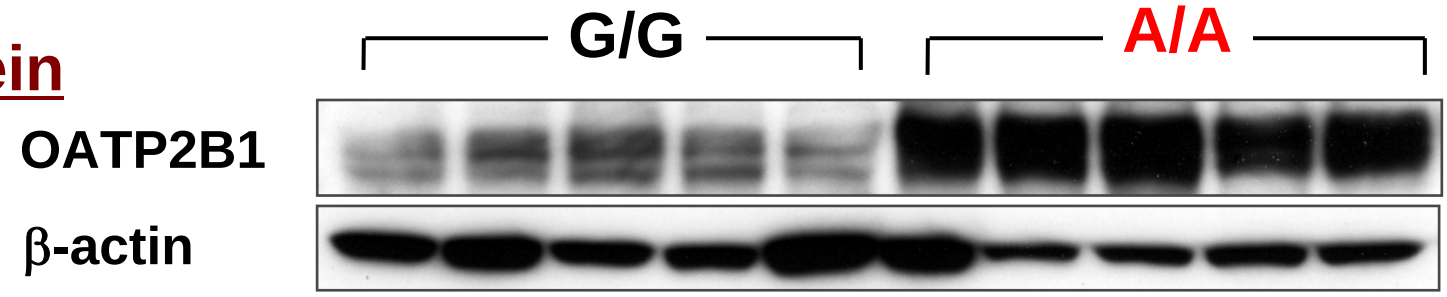
Gene	Tissue	n	rSNP	Expression	Allele Fre. (%)	Ref.
OCT1	Liver	109	None			AJP, 2008
OCT2	Kidney	63	-578_-576delAAG	Decreased	8.7	J. Hum. Genet., 2008
OAT1	Kidney	63	None			J. Hum. Genet., 2008
OAT2	Kidney	63	None			J. Hum. Genet., 2008
OAT3	Kidney	63	-659_-658ins, -578G>C, -515C>A, -461T>C, -32G>A	Unchanged	18.3 18.3, 15.9, 26.2, 1.6	J. Hum. Genet., 2008
OAT4	Kidney	63	-18C>T	Unchanged	3.2	J. Hum. Genet., 2008
MATE1	Kidney	109	**-32G>A**	Decreased	**1.8**	AJP, 2007
MRP2	Liver	102	-924G>A, -920A>G, -24C>T	Unchanged	30.9, 21.6, 21.6	Pharmacogenet. Genomics, 2009
OATP1B1	Liver	102	-868T>C, -815G>A, -617G>A, -318T>C, -93T>C	Unchanged	0.5, 10.8, 5.4, 5.4, 1.0	Pharmacogenet. Genomics, 2009
OATP1B3	Liver	102	-503T>C	Unchanged	1.0	Pharmacogenet. Genomics, 2009
OATP2B1	Liver	102	-916A>G, -835T>G, -747A>C, -730C>T, -618G>A, **-282G>A**, -89G>A	Unchanged -282G>A: Increased	0.5, 20.6, 32.4, 20.1, 23.8, **54.4**, 0.5	Pharmacogenet. Genomics, 2009

Effects of *OATP2B1* -282G>A on mRNA and Protein Expression

mRNA



Protein



Aoki et al., Pharmacogenet. Genomics, 19, 647-656 (2009)

rSNP (-32G>A) in the *MATE1* Gene

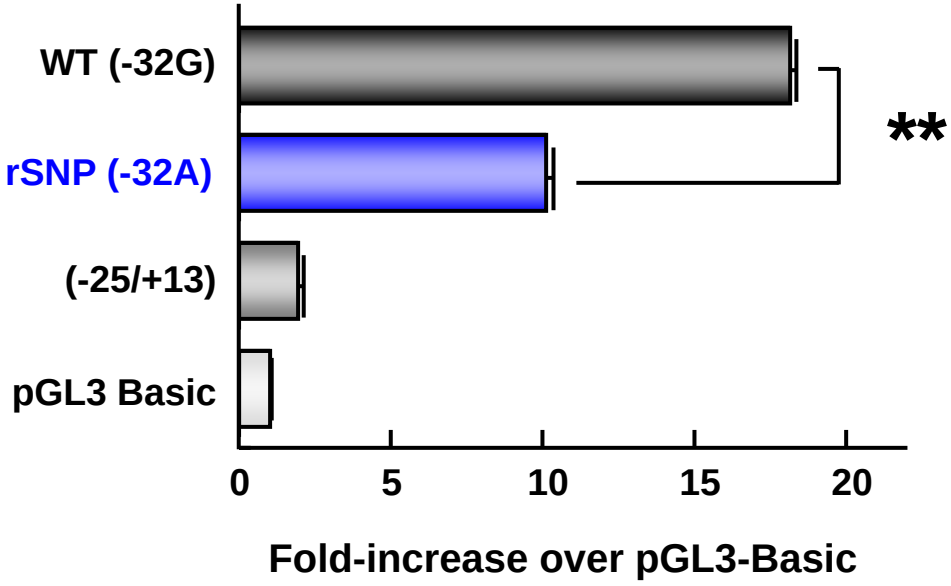
-32G>A rSNP

A

-47 GGCGGCCGGGGCGGGGACTG -28

GC Box
(Sp1 binding site)

Luciferase Assay

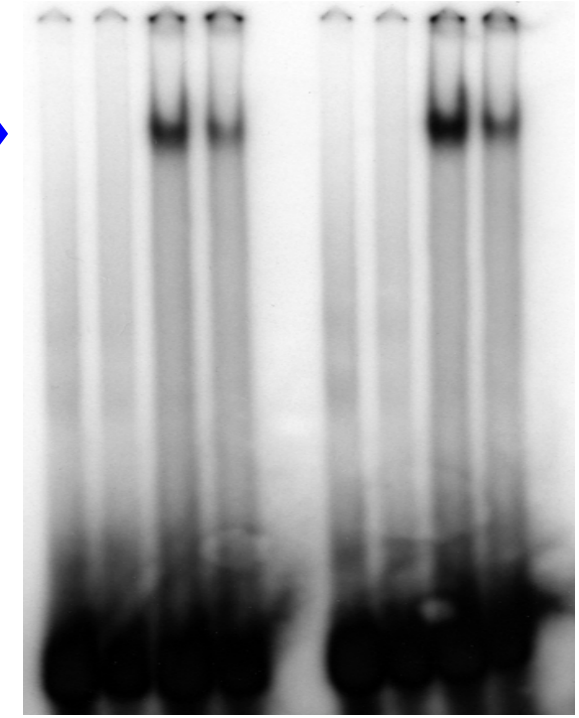


Kajiwara et al., *AJP.*, 293, F1564-F1570, 2007

Gel Shift Assay

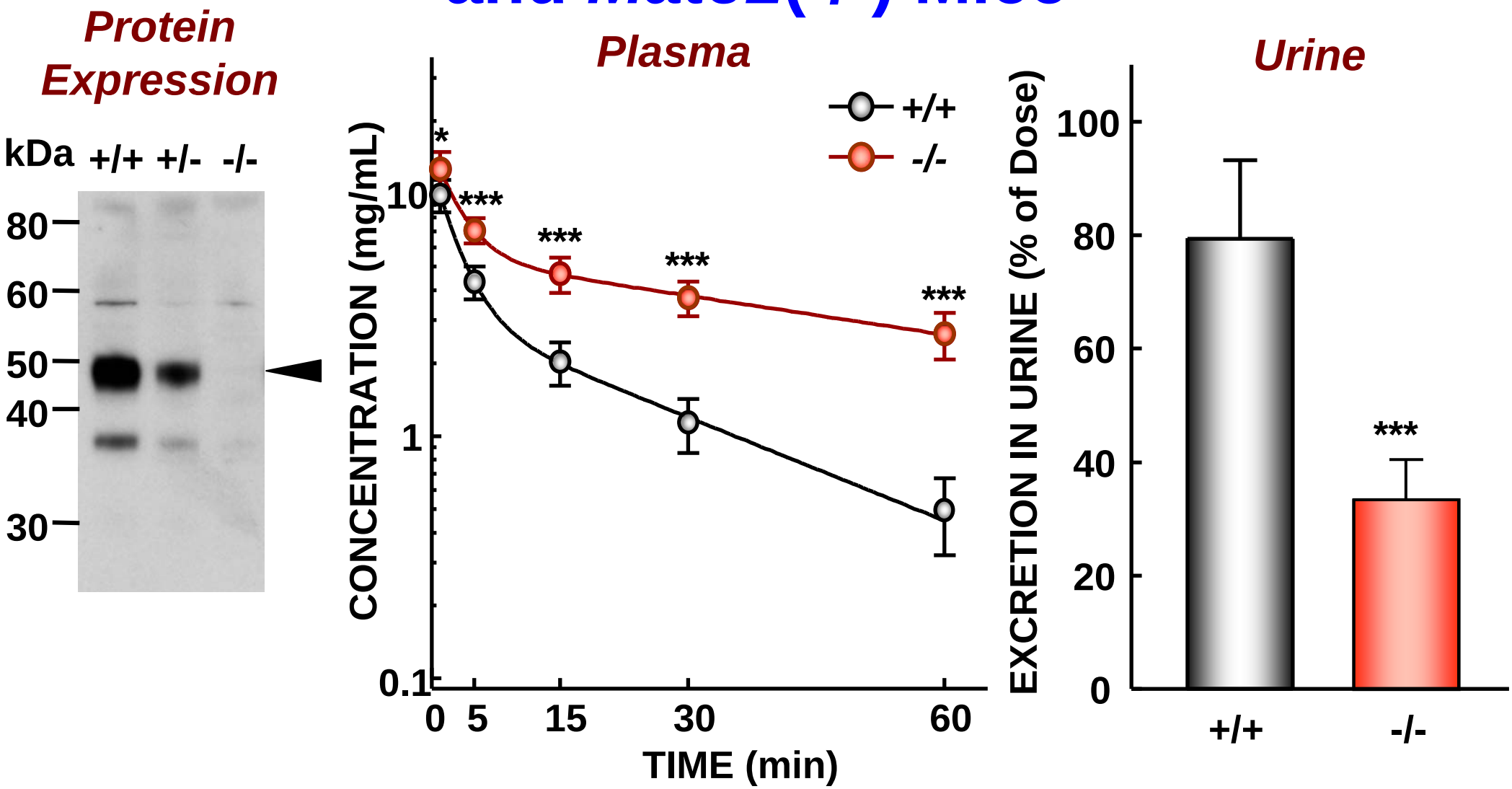
Wild probe B (-32G)	+		+		+		+		
SNP probe B (-32A)		+		+		+		+	
rhSp1 (ng)	0	0	90	90	0	0	120	120	

complex



G to A substitution downregulates the transcriptional activity of MATE1 by weakening the binding of Sp1.

Pharmacokinetics of Metformin in *Mate1*(+/+) and *Mate1*(-/-) Mice

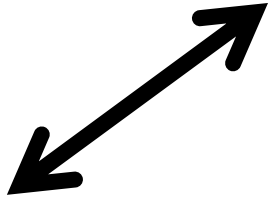


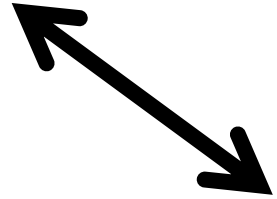
Tsuda et al., Mol. Pharmacol., 75, 1280-1286 (2009)

Expression of Drug Transporters are Controlled by Various Kinds of Regulation

Expressional Regulation of Drug Transporters

1) Transcription Factor
2) Epigenetic Regulation, 3) rSNP





Alterlation of Drug Conc.

Tissue-specific Expression

Interindividual Difference

Acknowledgements

Kyoto University Hospital

Department of Pharmacy

K. Inui (Present: Kyoto Pharmaceutical University)
H. Saito (Present: Kumamoto University Hospital)
M. Okuda (Present: Mie University Hospital)

T. Katsura, I. Yano, S. Masuda, H. Motohashi, M. Fukudo, A, Yonezawa, X. Pan, M. Irie, J. Shimakura, J. Asaka, M. Inoue, K. Ogasawara, M. Tsuda, M. Ueba, M. Kajiwara, H. Saito, J. Chen, T. Mizuno, M. Aoki, S. Watanabe

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I. Iwao, E. Hatano