Modeling Corticosteroid Pharmacogenomics and Proteomics in Rat Liver

Vivaswath S. Ayyar, Siddharth Sukumaran, Debra C. DuBois, Richard R. Almon, William J. Jusko

The Journal of Pharmacology and Experimental Therapeutics

TABLE S1. Evidence of micro RNA interactions with target genes and glucocorticoid-regulation of micro RNAs.

Species	Gene	miRNA	[a] Evidence for miRNA-gene interaction	Evidence for CS regulation of miRNA in cells lines or tissue
Rat	ACSL	miR-34a	RA, WB, qPCR	Yes (Belaya et al., 2018)
Mouse	ACTG1	miR-let7b	RA	No
Mouse	ARG1	miR-210	RA, qPCR	Yes (Martinez et al., 2017)
Mouse	ARG1	miR-33	RA, WB, qPCR	No
Mouse	ARG1	miR-296	WB	No
Mouse	ARG1	miR-676	WB	No
Mouse	ARG1	miR-382	WB	No
Mouse	ARG1	miR-669	WB	No
Mouse	ASS1	miR-22	qPCR	Yes (Wang et al., 2014)
Rat	CYP2E1	miR-212	RA	Yes (Balzano et al., 2017)
Rat	CYP2E1	miR-132	RA	Yes (Yue et al., 2018)
Mouse	ENPP1	miR-155	qPCR	Yes (Peshdary and Atlas, 2018)
Rat	GPX1	miR-181a	RA, WB, qPCR	Yes (Deng et al., 2016)
Mouse	GSTM1	miR-96	WB	Yes (Riester et al., 2012)
Mouse	HADHB	miR-124	RA, qPCR	Yes (Liang et al., 2017)
Rat	HNRNPK	miR-450a	WB	No
Rat	HSP90AA1	miR-1	WB	Yes (Shen et al., 2013)
Mouse	HSPA5	miR-181b	RA, WB, qPCR	No
Mouse	HSPA5	miR-30a	RA	Yes (Wu et al., 2014)
Rat	HSPA5	miR-378a	RA, qPCR	No
Rat	HSPA8	miR-17	RA	Yes (Smith et al., 2010)
Rat	HSPD1	miR-1	WB, qPCR	Yes (Shen et al., 2013)
Mouse	LDH1	miR-181b	RA, WB, qPCR	No
Mouse	LDHA	miR-449a	RA, WB, qPCR	Yes (Nemoto et al., 2013)
Rat	LDHA	miR-378a	RA, qPCR	No
Rat	MTCH2	miR-145	RA, WB	Yes (Shi et al., 2012)
Mouse	PDIA3	miR-330	RA, WB, qPCR	No
Mouse	PTBP1	miR-124	RA, qPCR	Yes (Liang et al., 2017)
Rat	TAT	miR-133a	RA, WB, qPCR	No

RA = reporter assay; WB = Western Blot; qPCR = quantitative PCR

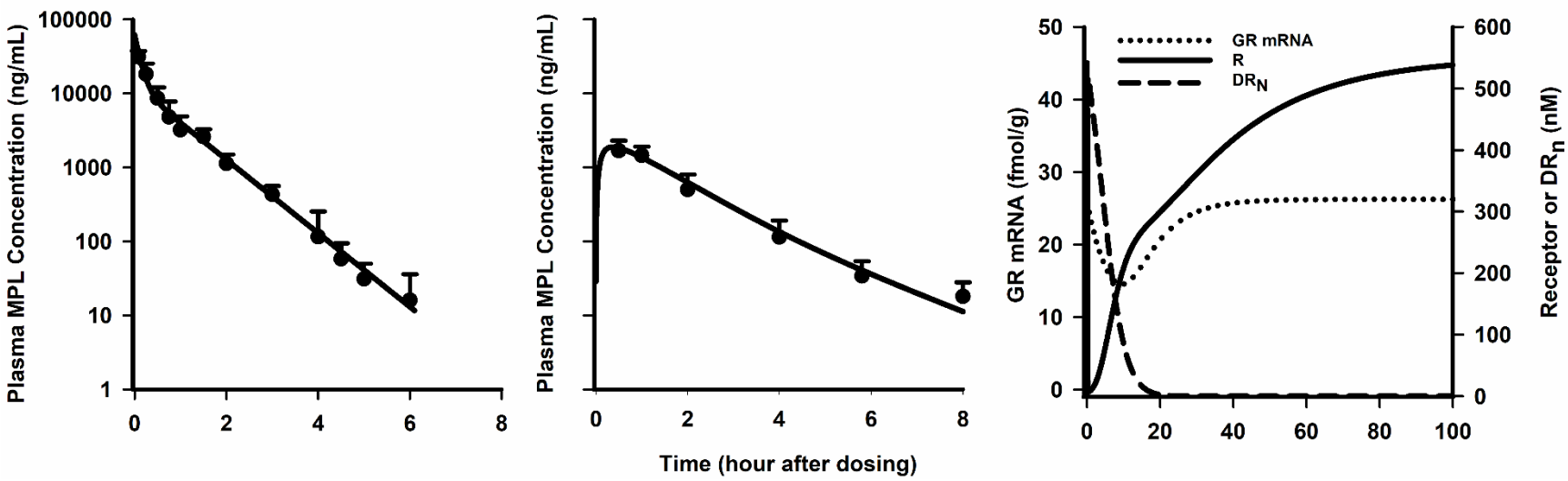
[a] Experimental method used to identify interaction (extracted from miRTarBase)

TABLE S2. Pharmacokinetic parameters for methylprednisolone (MPL) and glucocorticoid receptor (GR) dynamics.

Parameter (units)	Definition	Estimate (% CV)
MPL Pharmacokinetics		
$CL\ (L/h/kg)$	Clearance	2.93 (0.89)
$CL_D\ (L/h/kg)$	Distribution clearance	2.51 (1.94)
$V_c\ (L/kg)$	Central volume of distribution	0.803 (0.97)
$V_T\ (L/kg)$	Peripheral volume of distribution	0.974 (1.51)
F	Bioavailability	0.2 (0.94)
Fr	Fraction absorbed by k_{a1}	0.725 (fixed)
$k_{a1}\ (h^{-1})$	Absorption rate constant	1.82 (2.8)
$k_{a2}\ (h^{-1})$	Absorption rate constant	0.54 (4.1)
Glucocorticoid Receptor Dynamics [a]		
$k_{s,GRm}\ (fmol/g/h)$	Synthesis rate constant for GR mRNA	3.2
$k_{d,GRm}\ (h^{-1})$	Degradation rate constant for GR mRNA	0.12
$k_{s,GR}\ (nM/h)(fmol/g)^{-1}$	Synthesis rate constant for receptor	0.84
$IC_{50,GRm}\ (nM)$	DR_n for 50% inhibition of GR mRNA synthesis	123.7
$k_{d,GR}\ (h^{-1})$	Degradation rate constant for receptor	0.04
$k_{on}\ (nM^{-1}\cdot h^{-1})$	Association rate constant	0.019
f_{mpl}	Unbound fraction of MPL	0.23
$k_{re}\ (h^{-1})$	DR_n loss rate constant	0.402
R_f	Fraction recycled	0.69
$k_T\ (h^{-1})$	Translocation rate constant	58.2
$GR_m\ (0)\ (fmol/g)$	GR mRNA initial concentration	25.8
$GR(0)\ (nM)$	Free cytosolic receptor initial concentration	540.7
$DR(0)\ (nM)$	Drug-receptor complex initial concentration	0
$DR_n(0)\ (nM)$	Nuclear complex initial concentration	0

[a] Parameter values obtained from Hazra et al. (2007a)

Figure S1. Simultaneous fitting results of MPL pharmacokinetics in plasma (Eqs. 1-3) upon administration of 50 mg/kg intravenous (IV) injection of MPL (left panel) and following 50 mg/kg intramuscular (IM) injection (center panel). Solid lines represent model fittings, circles are means, and error bars are 1 standard deviation (SD) (n = 3 – 6 rats per point). Simulated profiles of the driving forces (GR mRNA, free cytosolic receptor, and drug-receptor complex in the nucleus) controlling the gene-mediated effects of CS. Simulations are based on the model in Fig. 2. The parameters used are for MPL effects as listed in Table S2.



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