Supplementary Materials and Methods

Supplementary Table 1: Nocturnal HPA Axis Model Parameters Common to Both Sexes

Parameter	Value	Description
k_{p1}	0.3819 μMh^{-1}	Estimated, zero order synthesis rate constant of CRH
V_{d1}	0.3492 μMh^{-1}	Estimated, first order rate constant for CRH degradation
K_{d1}	4.3875 μM	Estimated, Michaelis-Menten constant for CRH degradation
k_{p2}	0.4561 μMh^{-1}	Estimated, first order rate constant for synthesis of ACTH
V_{d2}	1.0015 μMh^{-1}	Estimated, first order rate constant for degradation of ACTH
K_{d2}	0.8488 μM	Estimated, Michaelis-Menten constant for ACTH degradation
V_{d3}	0.7245 μMh^{-1}	Estimated, first order rate constant for CORT degradation
K_{d3}	0.1807 μM	Estimated, Michaelis-Menten constant for CORT degradation
$GR(0)$	540.7 nmol L^{-1} mg protein^{-1}	Initial GR content, [47]
$GR_{mRNA}(0)$	25.8 fmolg^{-1}	Initial GR mRNA content, [47]
$k_{syn_{GRm}}$	2.9 fmolg^{-1} h^{-1}	Zero order rate constant for synthesis of GR mRNA, [47]
r_f	0.49	GR recycle fraction from nucleus to cytoplasm, [47]
k_{re}	0.57 h^{-1}	Rate of GR recycling from nucleus to cytoplasm, [47]
k_{on}	0.00329 L nmol^{-1} h^{-1}	Second-order rate constant for CORT-GR binding, [47]
$k_{deg,GRm}$	$k_{syn_{GRm}}/GR_{mRNA}(0)$	First-order rate constant for degradation of GR mRNA, [47]
$k_{deg,GR}$	0.0572 h^{-1}	First order rate constant for degradation of GR, [47]
$k_{syn,GR}$	$GR(0).k_{deg,GR}/\ GR_{mRNA}(0)$	First order rate constant for synthesis of GR, [47]
k_T	0.63 h^{-1}	Rate of GR translocation from cytoplasm to nucleus, [47]
k_{imp}	0.5	Strength of ACTH impulse
$k_{stress.out}$	6.79 h^{-1}	Rate constant for clearance of stressor

k_s	40 a.u.	Strength of induction of CRH production by stressor
k_t	0.92 a.u.	Estimated, rate constant for light transduction
k_{us}	1 a.u.	Estimated, rate constant for production of light effect
n	2 a.u.	Estimated, Hill coefficient for light effect
$k_{deg,us}$	0.92 a.u.	Estimated, rate constant for degradation for light effect
k_{eff}	24 a.u.	Estimated, strength of induction of light-effect degradation
k_a	0.42 hr^{-1}	First-order absorption rate constant for PNL [48]
k_e	0.33 hr^{-1}	First-order elimination rate constant for PNL [48]
k_{t1},k_{t2},k_{t3},k_{t4},k_{t5}	1 hr^{-1}	Rate constants for transfer between transit compartments

Abbreviations: a.u. - arbitrary units; mRNA – messenger RNA

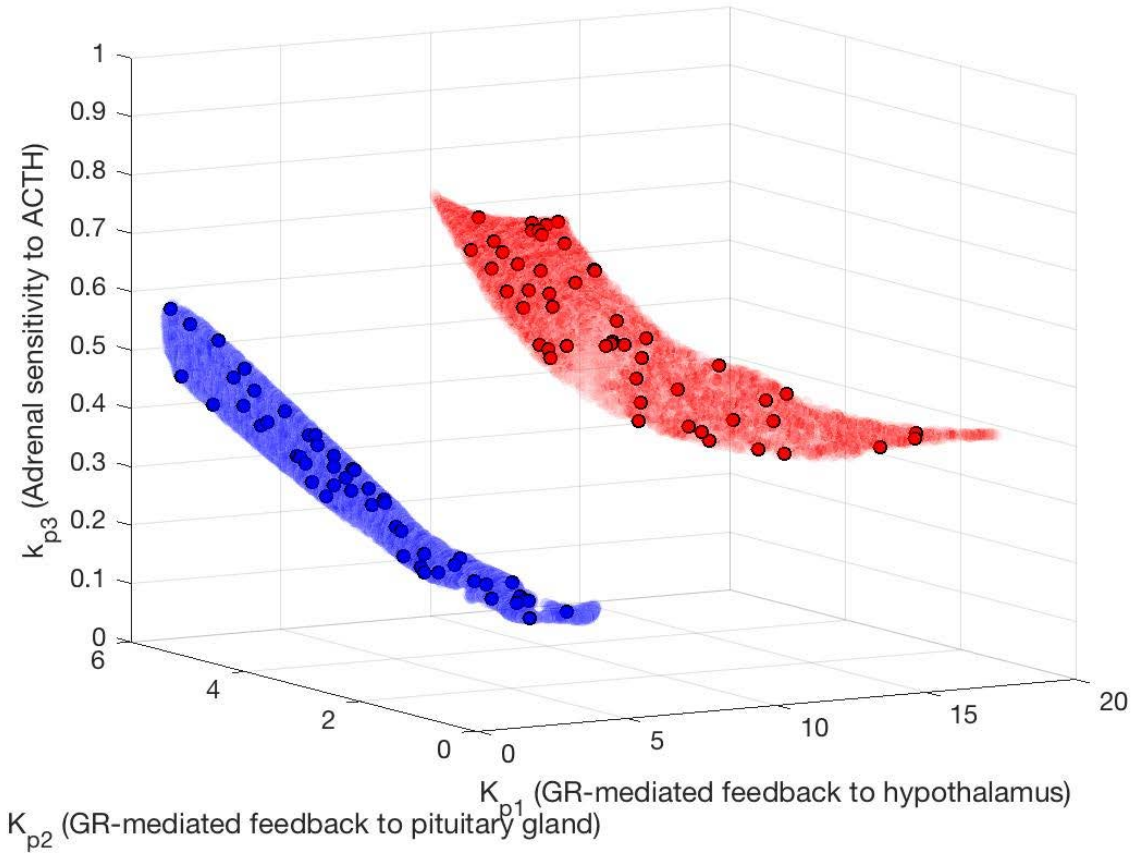

Figure S1: Male and female parameter subspaces for sex-specific parameters used in dosing experiments. An example subpopulation of 50 male rats and 50 female rats selected from the original population established by Rao et al. is shown [30].

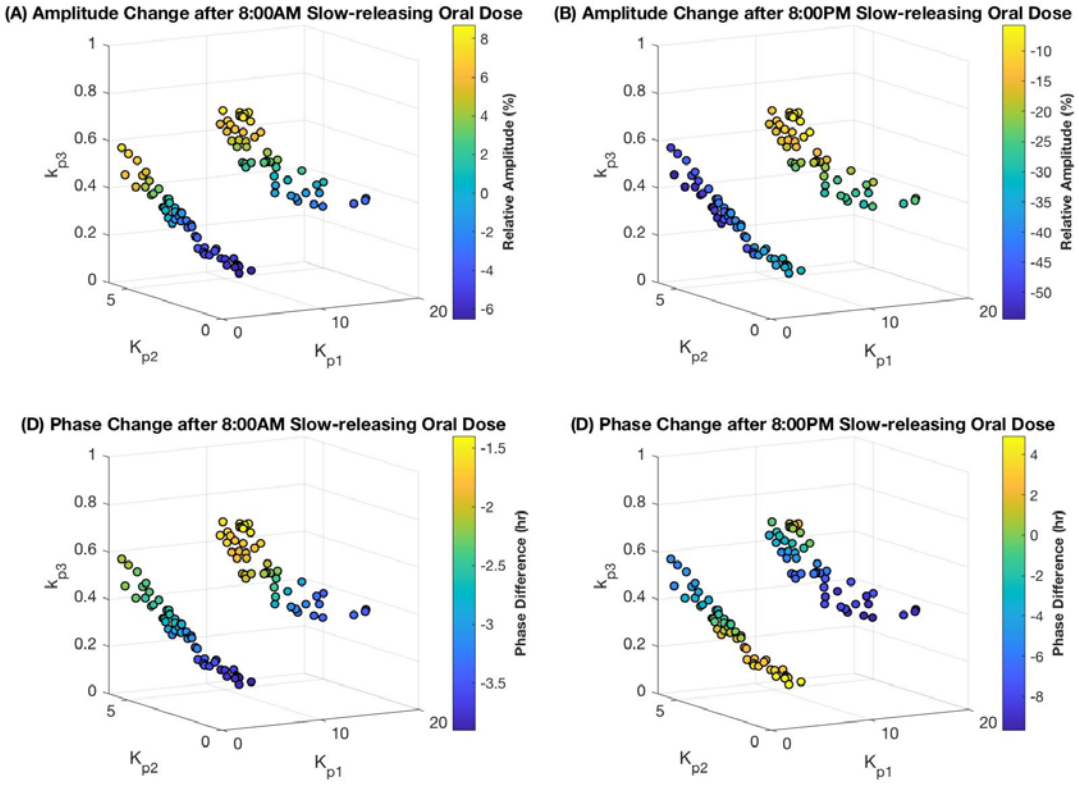

Figure S2: Amplitude and phase of the modified corticosterone rhythm after chronic once-daily administration of the slow-releasing glucocorticoid at 8:00 AM and 8:00 PM in male and female rats under nominal conditions. The relative amplitude and phase difference for the modified corticosterone rhythms are given for each individual defined by three sex-dependent parameters.

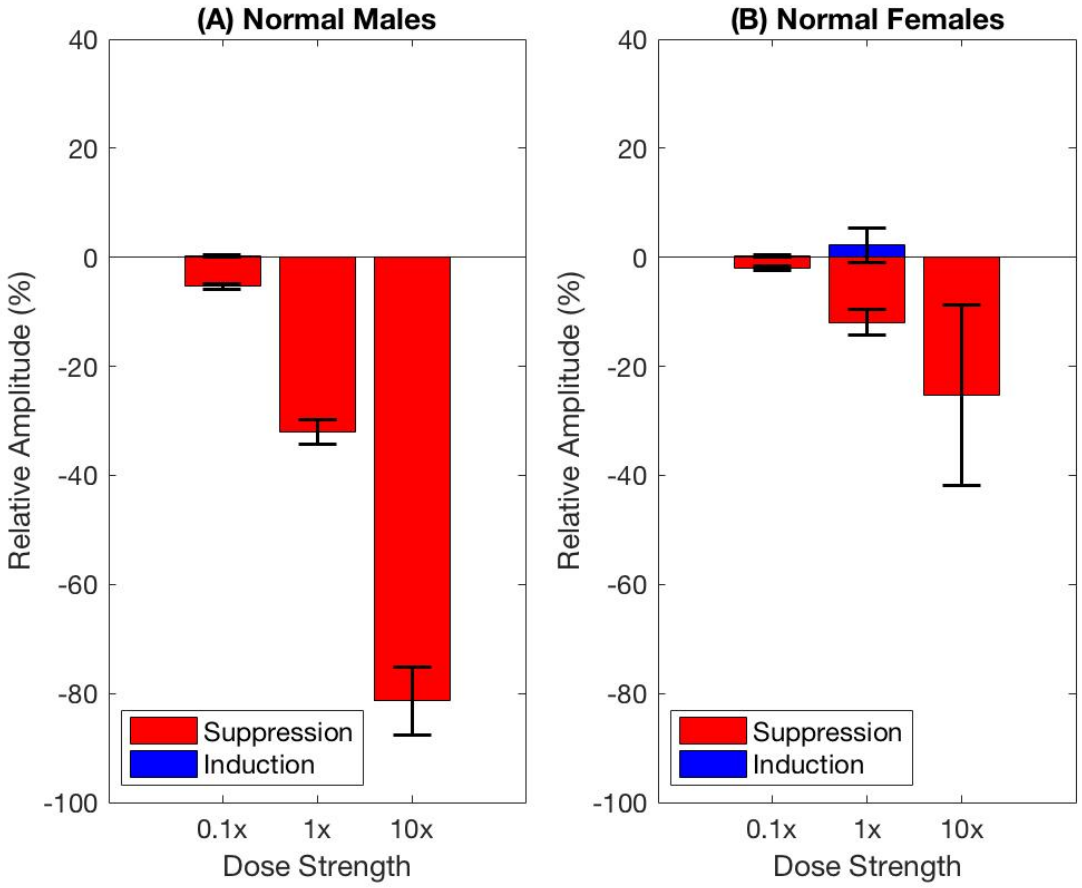

Figure S3: Influence of dosing strength on the amplitude of the modified corticosterone rhythm following chronic once-daily administration of slow-releasing glucocorticoids in male and female rats under nominal conditions. The amplitude is given for the dosing times which resulted in the greatest inductive and suppressive effects at each strength in male rats (A) and female rats (B). The error bars represent ±1 standard deviation of the population mean for amplitude and phase changes.

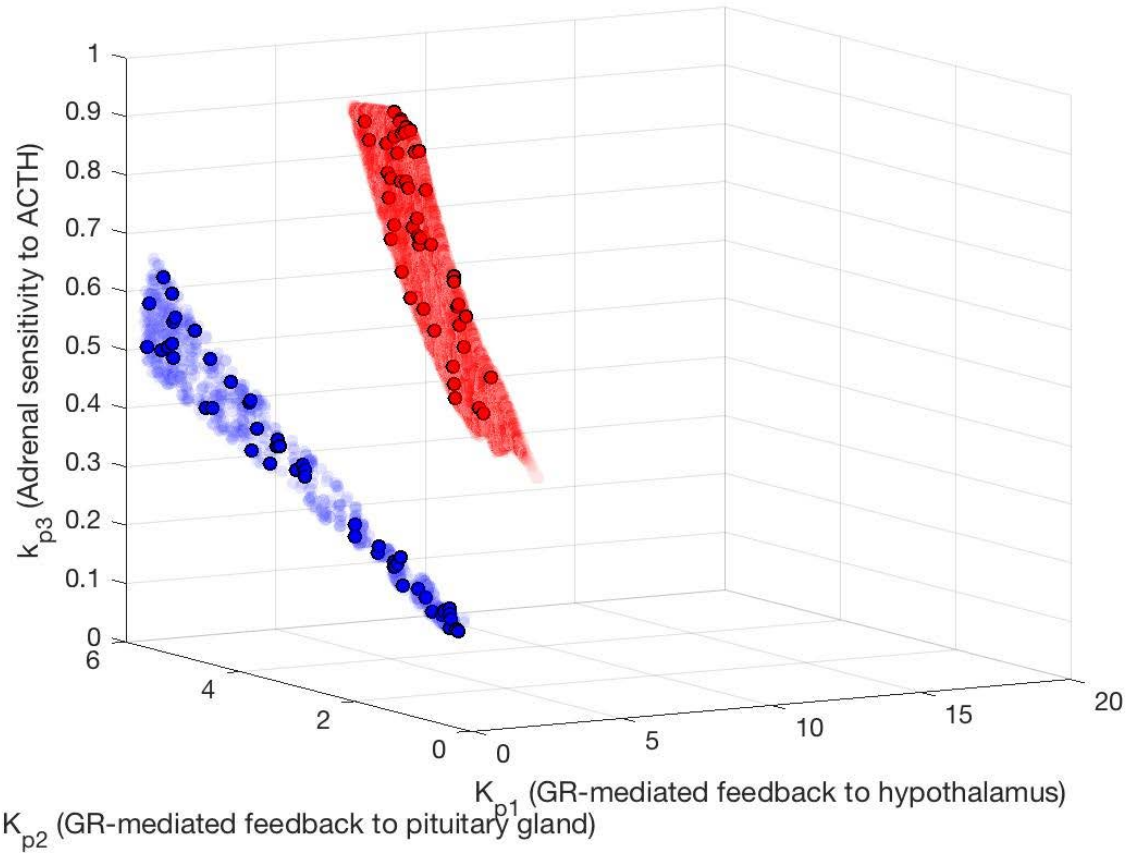

Figure S4: Chronically stressed male and female parameter subspaces for sex-specific parameters used in dosing experiments. An example subpopulation of 50 male rats and 50 female rats selected from the high stress populations established by Rao et al. is shown [30].

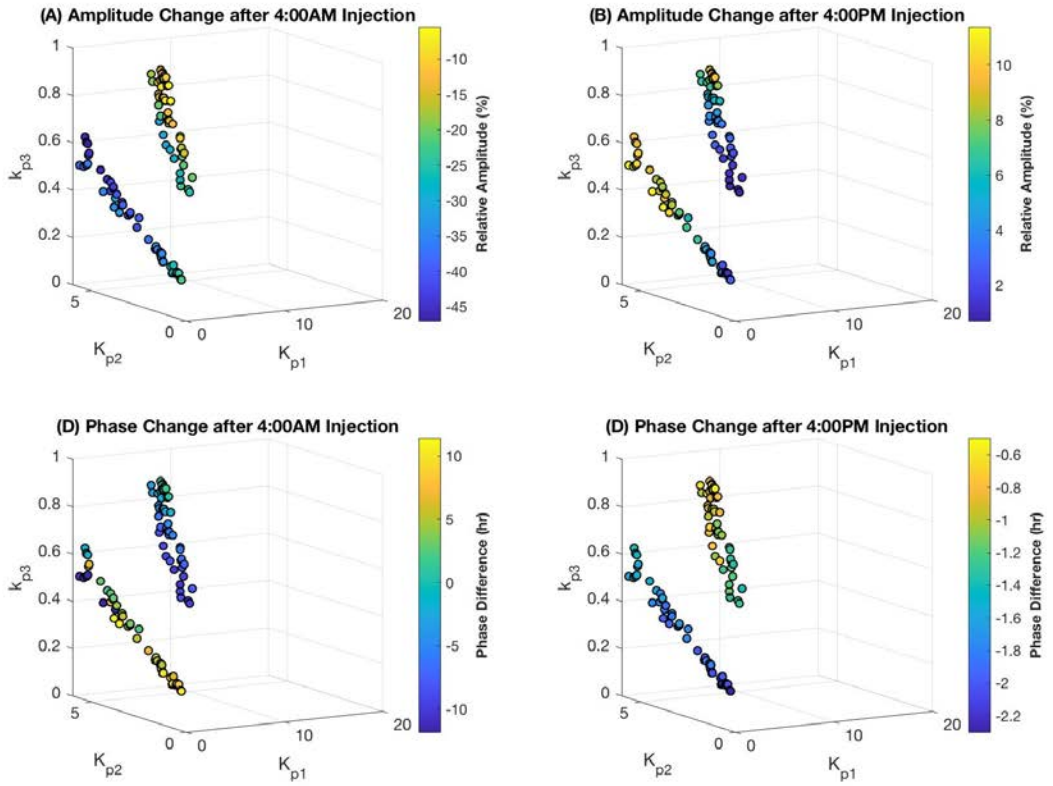

Figure S5: Amplitude and phase of the modified corticosterone rhythm after chronic once-daily IV bolus administration of glucocorticoids at 4:00 AM and 4:00 PM in male and female rats under stressed conditions. The relative amplitude and phase difference for the modified corticosterone rhythms are given for each individual defined by three sex-dependent parameters.

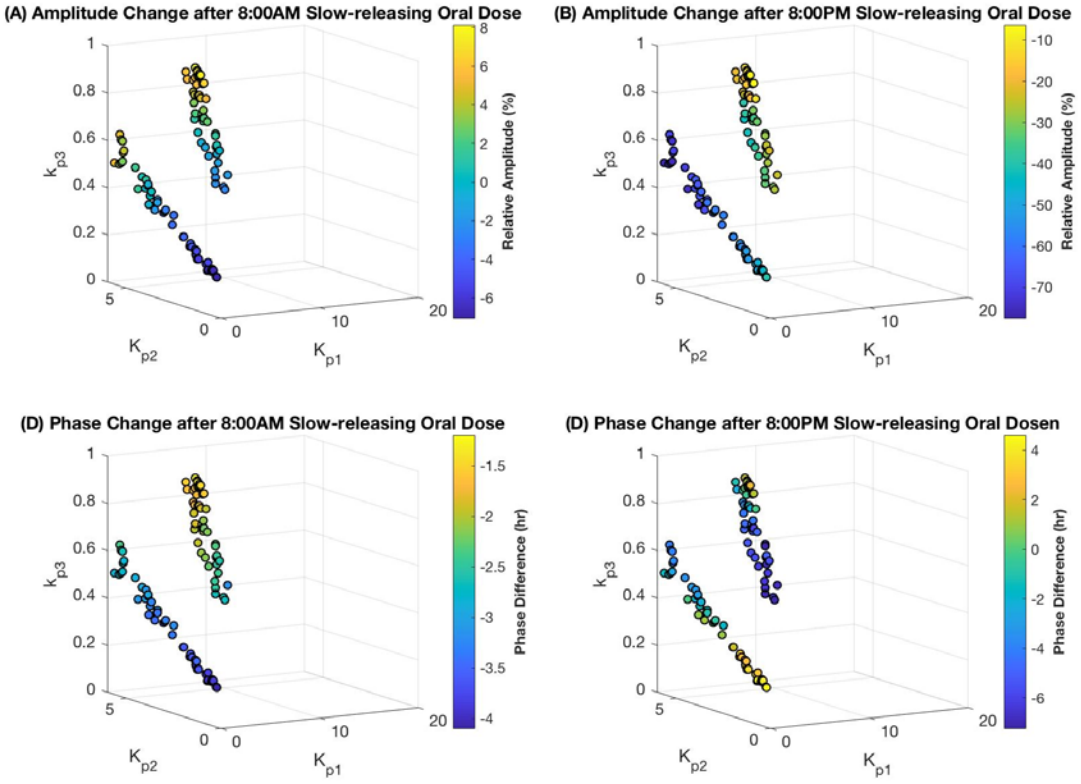

Figure S6: Amplitude and phase of the modified corticosterone rhythm after chronic once-daily administration of the slow-releasing glucocorticoid at 8:00 AM and 8:00 PM in male and female rats under stressed conditions. The relative amplitude and phase difference for the modified corticosterone rhythms are given for each individual defined by three sex-dependent parameters.

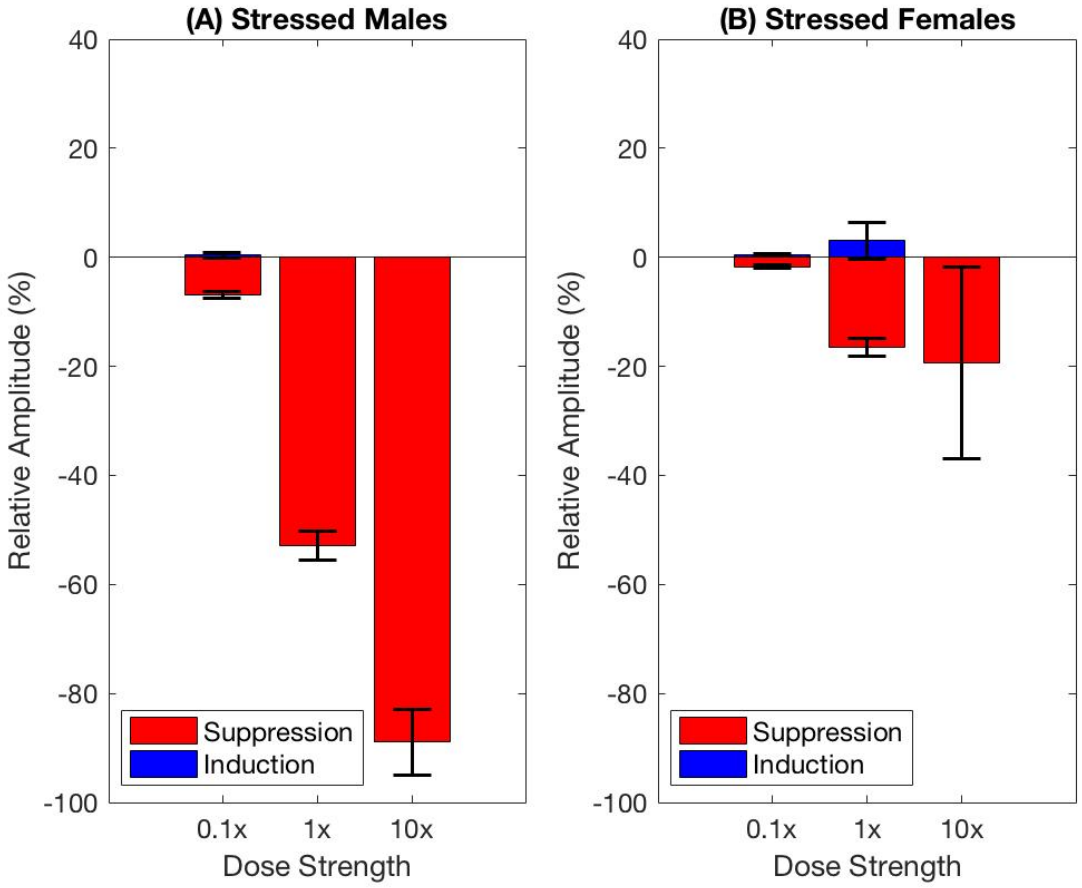

Figure S7: Influence of dosing strength on the amplitude of the modified corticosterone rhythm following chronic once-daily administration of slow-releasing glucocorticoids in male and female rats under stressed conditions. The amplitude is given for the dosing times which resulted in the greatest inductive and suppressive effects at each strength in male rats (A) and female rats (B). The error bars represent ±1 standard deviation of the population mean for amplitude and phase changes.