Supplemental Figure 1. Effects of caffeine on sleep over 7 days. Sleep profile plotted in 30 minute bins for female flies fed no caffeine (open diamonds, n=64) or 0.5 mg/ml caffeine (closed squares, n=64 flies). Gray bars and black bars represent subjective day and night, respectively.

Supplemental Figure 2. Effects of caffeine on sleep in L:D. Daily sleep time (*A*), sleep bout number (*B*), sleep bout duration (*C*), and daily, day-time, and night-time activity/waking minute (*D*) are shown for female flies fed no caffeine (white, n=31) or 0.5 mg/ml caffeine (black, n=31) in L:D. Data from the same flies is shown for *A*-*D*. ** indicates $p<0.01$ and *** indicates $p<0.001$, compared to no caffeine treatment.

Supplemental Figure 3. *dAdoR* is not required for baseline sleep. Daytime and nighttime sleep time (*A*), sleep bout number (*B*), and sleep bout duration (*C*). Activity/waking minute (*D*) is shown for control (n=64), *dAdoR* (n=64), control/*Df(3R)Exel6214* (n=70) and *dAdoR*/*Df(3R)Exel6214* (n=68) female flies. Control and control/*Df(3R)Exel6214* are denoted by white bars, while *dAdoR* and *dAdoR*/*Df(3R)Exel6214* are denoted by black bars and gray bars, respectively. Data from the same flies are shown for *A*-*C*. * denotes $p<0.05$.

Supplemental Figure 4. *dAdoR* is not required for rebound sleep or reduction of sleep latency following sleep deprivation. *A*, Amount of sleep lost in minutes (dep) expressed as a percentage relative to sleep time for unshaken controls during the 6 hr mechanical deprivation (ZT18-ZT24) and amount of sleep rebound in minutes expressed as a

percentage relative to amount of sleep lost (reb) during the 6 hr recovery period (ZT0-6) of the third day is shown for control/*Df(3R)Exel6214* (white, n=42) and for *dAdoR*/*Df(3R)Exel6214* (black, n=18) female flies. *B*, Reduction in sleep latency following deprivation, compared to undisturbed controls for control/*Df(3R)Exel6214* (white) and *dAdoR*/*Df(3R)Exel6214* (black) female flies.

Supplemental Figure 5. *dAdoR* is not required for the effects of caffeine on sleep and circadian period. Daily sleep time (*A*) and period (*B*) are shown for control/*Df(3R)Exel6214* and *dAdoR*/*Df(3R)Exel6214* female flies. For daily sleep time, n=38 (no caffeine) and n=39 (0.5 mg/ml caffeine) for control/*Df(3R)Exel6214,* and n=32 (no caffeine) and n=33 (0.5 mg/ml caffeine) for *dAdoR*/*Df(3R)Exel6214* female flies. For circadian period, n=57 (no caffeine) and n=55 (0.5 mg/ml caffeine) for control/*Df(3R)Exel6214,* and n=42 (no caffeine) and n=40 (0.5 mg/ml caffeine) for *dAdoR*/*Df(3R)Exel6214* female flies. Analysis by two-factor ANOVAs revealed no interaction between genotype and caffeine dose for daily sleep or period length. There was no main effect of genotype on sleep time or period length. A significant main effect of caffeine dose on daily sleep and period was observed, and significance by post-hoc Tukey HSD tests is shown. control/*Df(3R)Exel6214* and *dAdoR*/*Df(3R)Exel6214* are denoted by white bars and black bars, respectively. *** indicates $p<0.001$ compared to no caffeine treatment.

Supplemental Figure 6. Other methylxanthines can also reduce sleep in wild-type and *dAdoR* flies. *A,* Daily sleep time for wild-type control (ctrl) and *dAdoR* female flies fed

CPT (+) or no drug (-). For control, n=23 and 20 for no drug and + CPT, respectively. For *dAdoR*, n=22 and 22 for no drug and + CPT, respectively. *B,* Daily sleep time for control vs *dAdoR* female flies fed 0.3 mg/ml DMPX (+) or no drug (-). For control, n=17 and 15 for no drug and + DMPX, respectively. For *dAdoR*, n=23 and 19 for no drug and + DMPX, respectively. * and ** indicate $p<0.05$ and $p<0.01$, respectively.

Supplemental Table 1. The effect of caffeine on sleep in wild-type (*RC1*) male flies. ** indicates p<0.01 and *** indicates p<0.001.

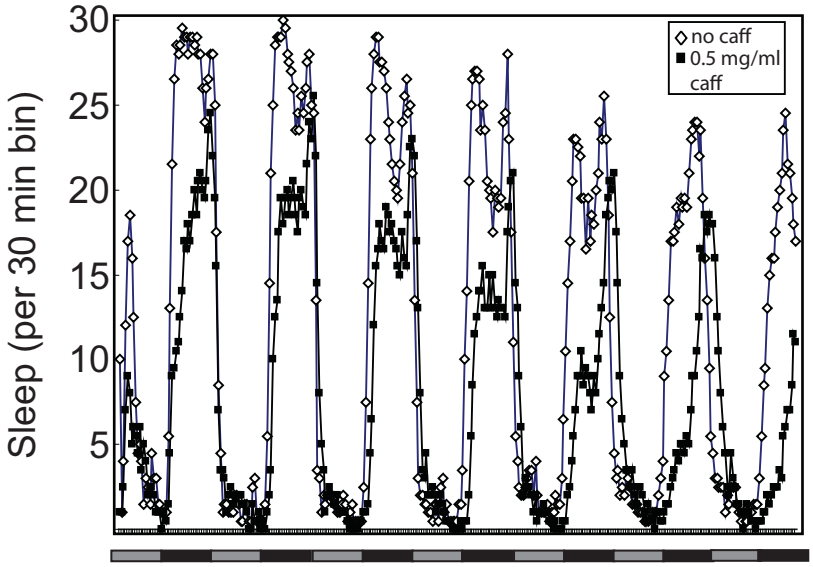
Caffeine dose (mg/ml)	**0**	**0.1**	**0.2**	**0.5**
n=	32	32	32	32
Daily sleep (min)	650.4 ±37.8	425.9±39.4***	241.9±28.4***	253.3±23.5***
Sleep Bout Number	18.9±1.5	16.4±1.2	10.6±1.0***	15.3±1.2
Sleep bout duration (min)	44.4±5.0	26.9±2.4**	23.2±2.9***	18.9±3.0***
Activity/min awake	3.0±0.1	3.2±0.1	2.9±0.1	3.2±0.1

Supplemental Table 2. Most significant hits detected by BLAST in a *D. melanogaster* protein database (Flybase) using the human A2A adenosine receptor open reading frame.

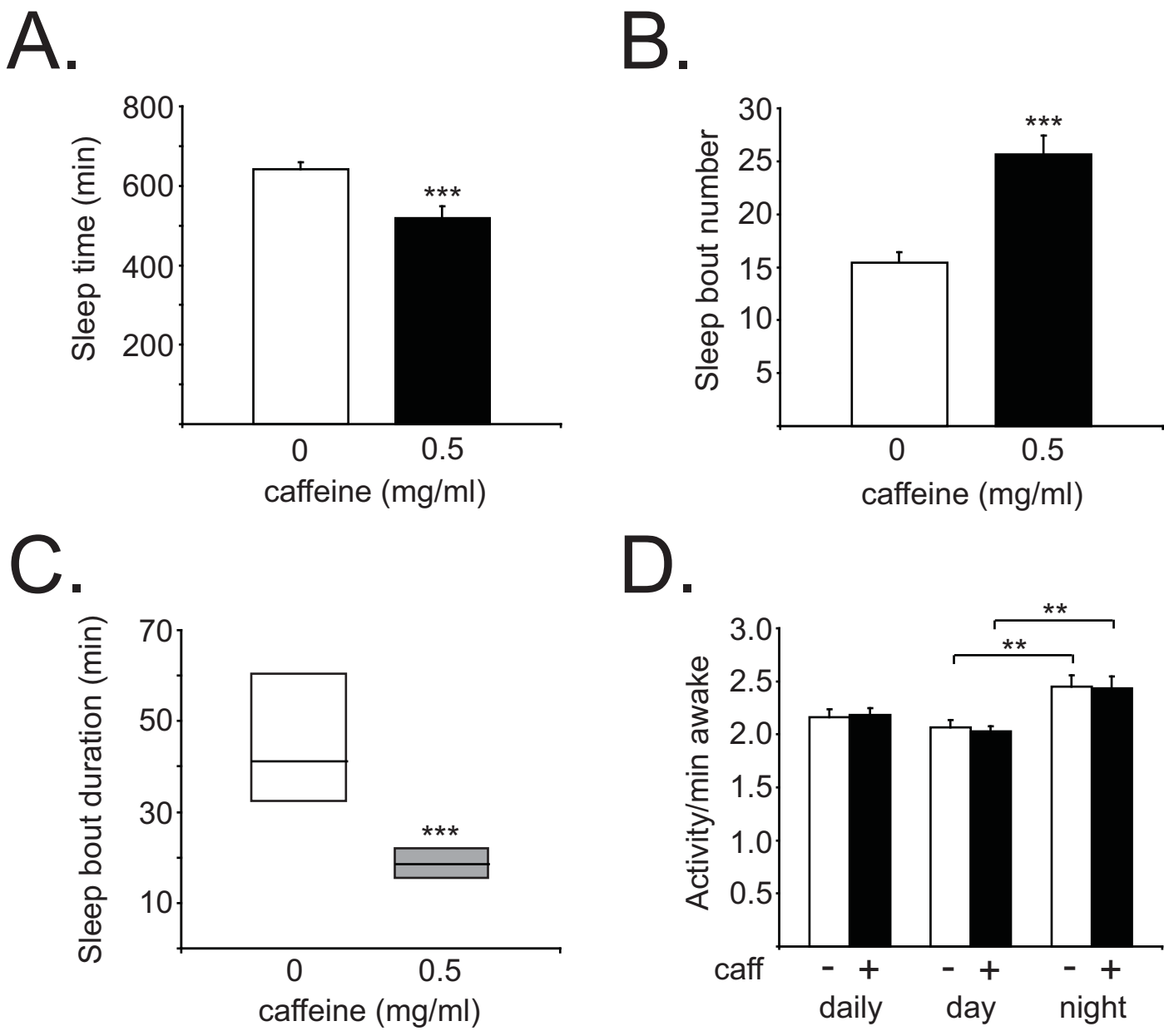
Gene name	**E value**
Adenosine receptor (*CG9753*)	4.3e-42
Octopamine receptor 2 (*CG6919*), isoform A	4.3e-20
Octopamine receptor 2 (*CG6919*), isoform B	1.5e-19
Octopamine ß3R receptor (*CG4244*), isoform D	1.5e-19
Octopamine ß2R (*CG33976*)	2.3e-18
Dopamine receptor (*CG9652*), isoform B	7.0e-18

Supplemental Table 3. Most significant hits detected by BLAST in a *D. melanogaster* protein database (Flybase) using the human A1 adenosine receptor open reading frame.

Gene name	**E value**
Adenosine receptor (*CG9753*)	4.9e-25
Octopamine receptor 2, (*CG6919*), isoform A	4.3e-11
Octopamine receptor 2, (*CG6919*), isoform B	5.8e-11
Tyramine receptor, (*CG7485*)	2.4e-10
Octopamine ß3R receptor (*CG4244*), isoform D	8.5e-10
Octopamine receptor in mushroom bodies, (*CG3856*), isoform C	1.4e-9



SUPP FIGURE 1 -WU



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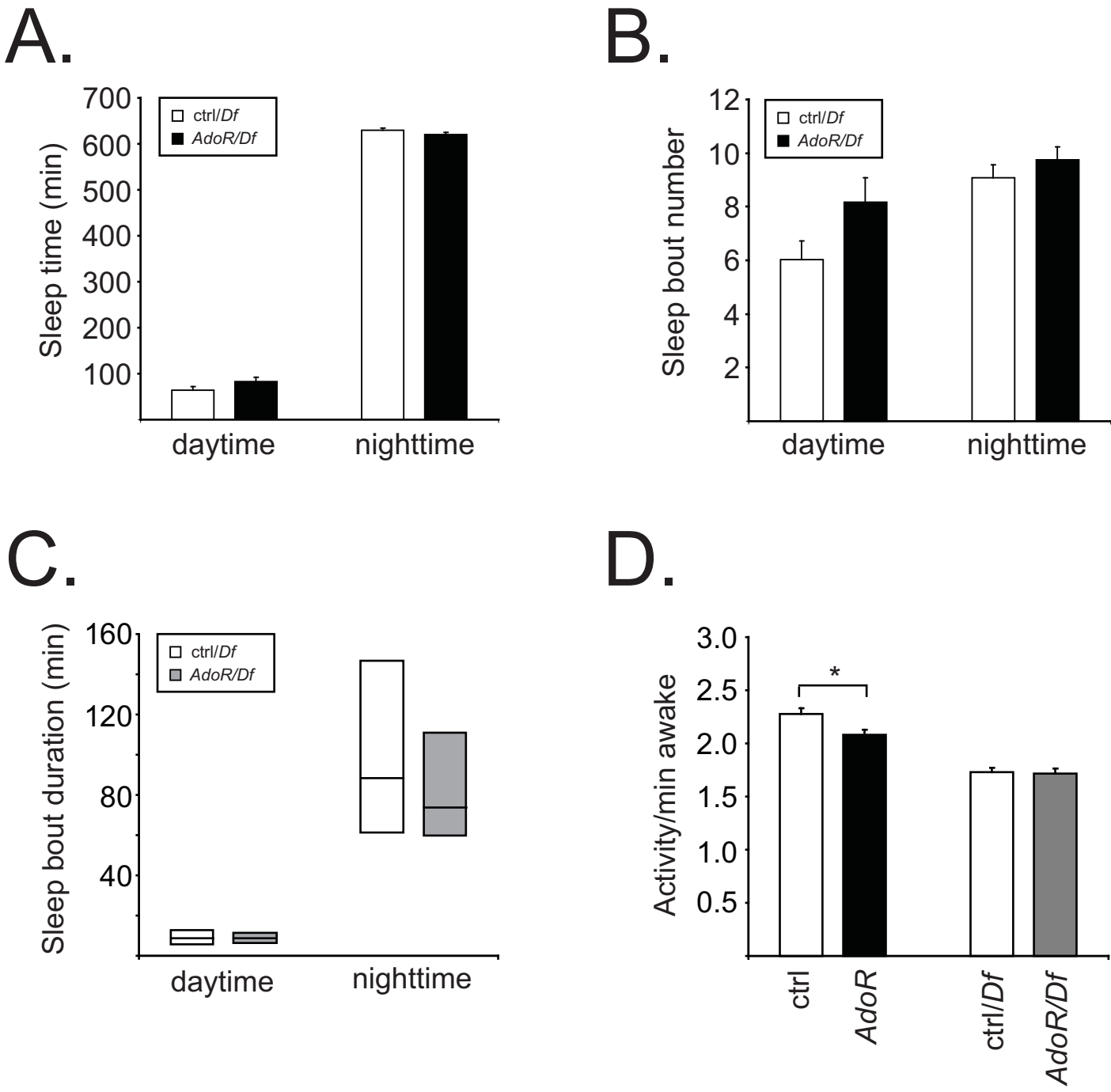

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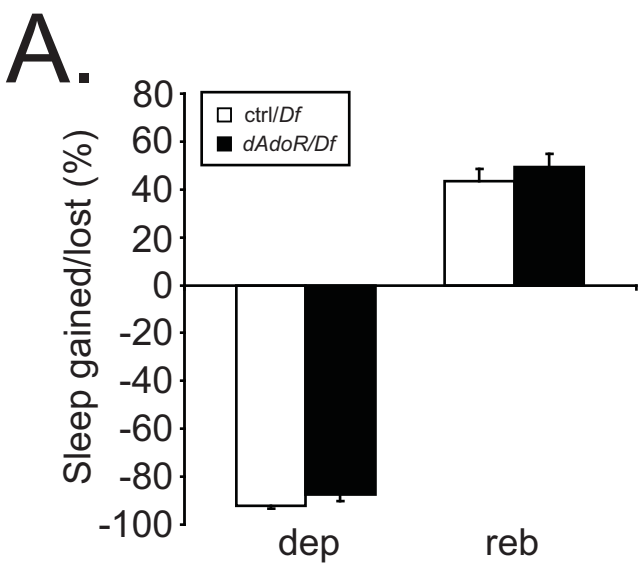

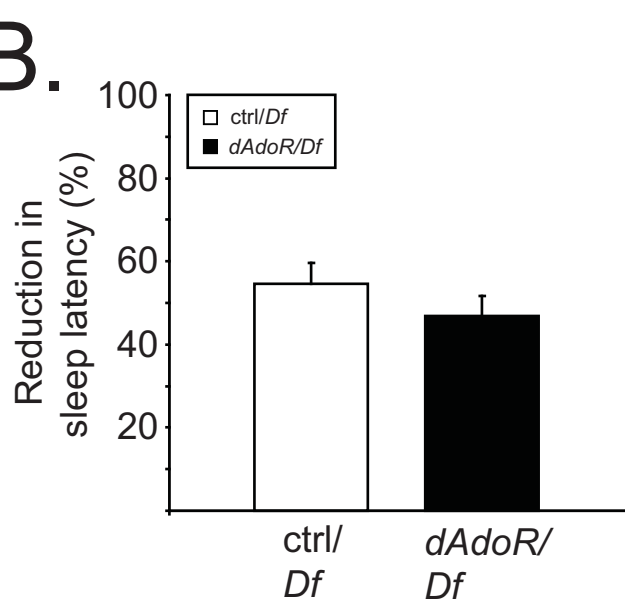

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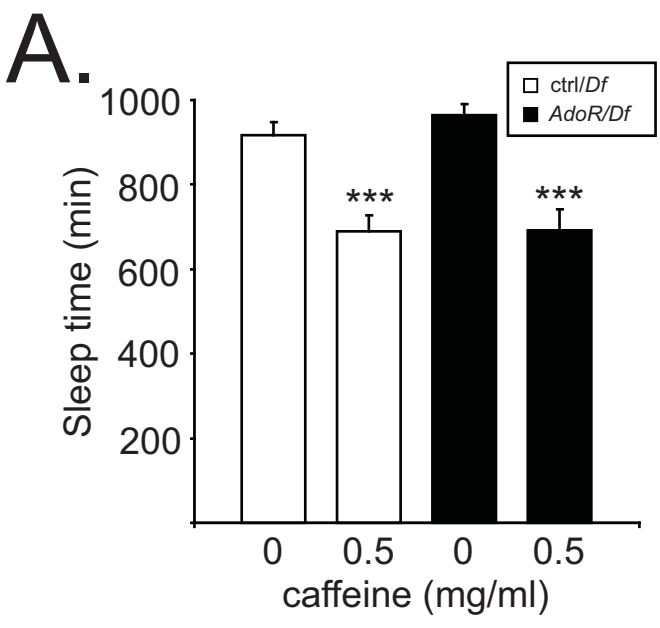
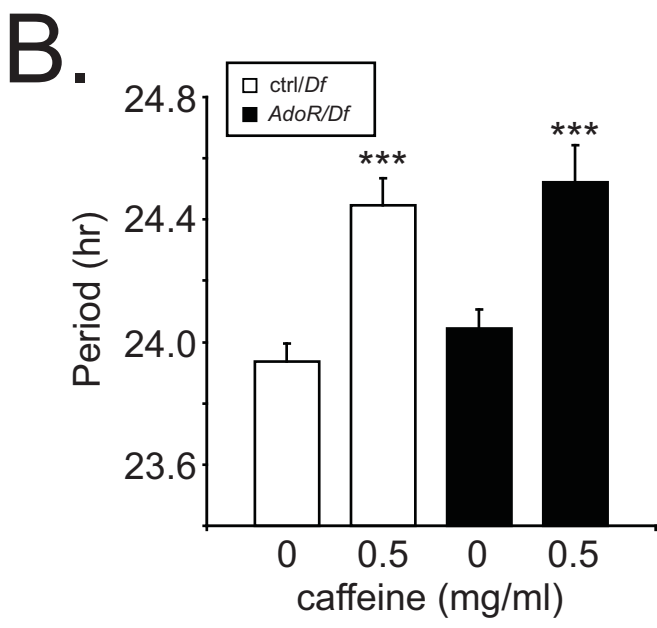
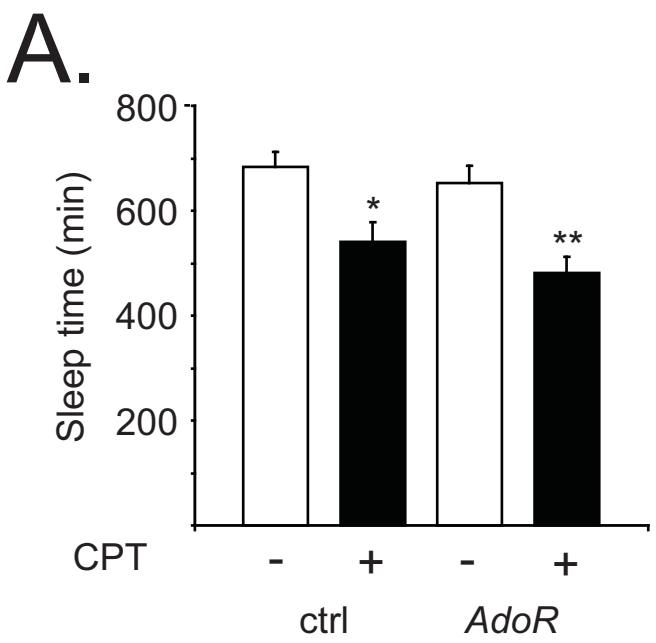
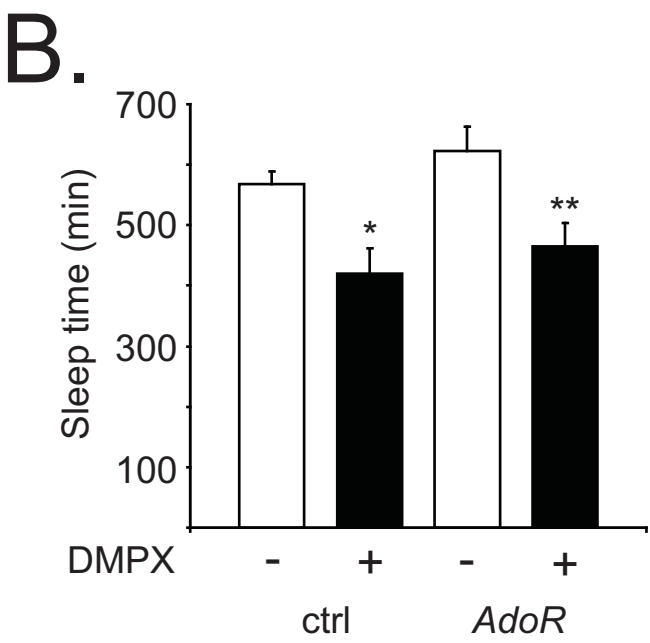




SUPP FIGURE 5-WU





SUPP FIGURE 6-WU