

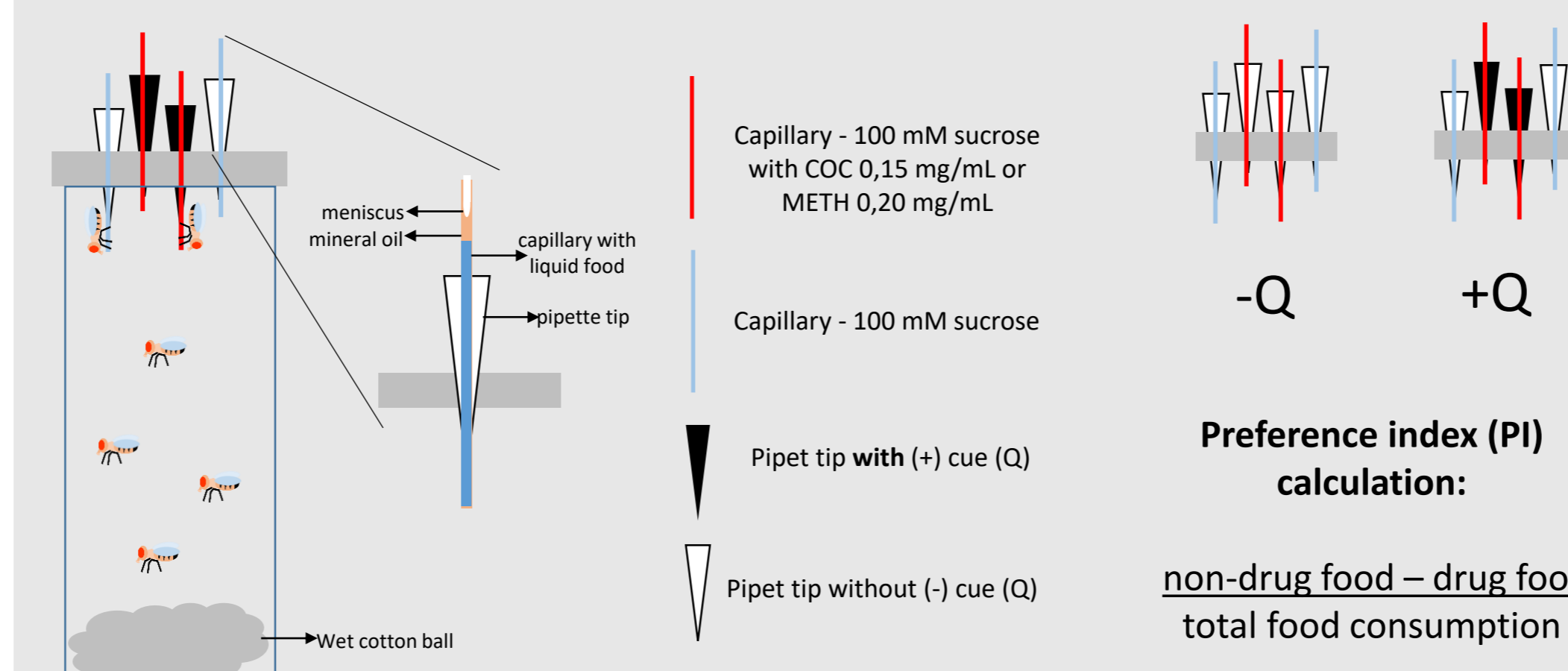
Introduction

Drosophila preferentially consumes ethanol-containing food, but it is not known if psychostimulants, such as cocaine (COC) and methamphetamine (METH), bitter compounds with no nutritional relevance, can induce preferential consumption.

If *Drosophila* preferentially consumes COC or METH-containing food it would indicate that drug activates motivational and/or reward circuits. This would allow for an unbiased gene discovery for genes involved in preferential drug consumption.

Methods

To test if flies will voluntarily self-administer psychostimulants we used the two-choice Capillary Feeder (CAFE) assay, where flies can choose between capillaries with drug- or a non-drug containing food. Capillaries were changed daily for 4-5 days.



We measured:

a) Preferential consumption for COC and METH

b) Features of addiction:

- consumption against negative consequence (quinine)
- relapse induced by drug deprivation

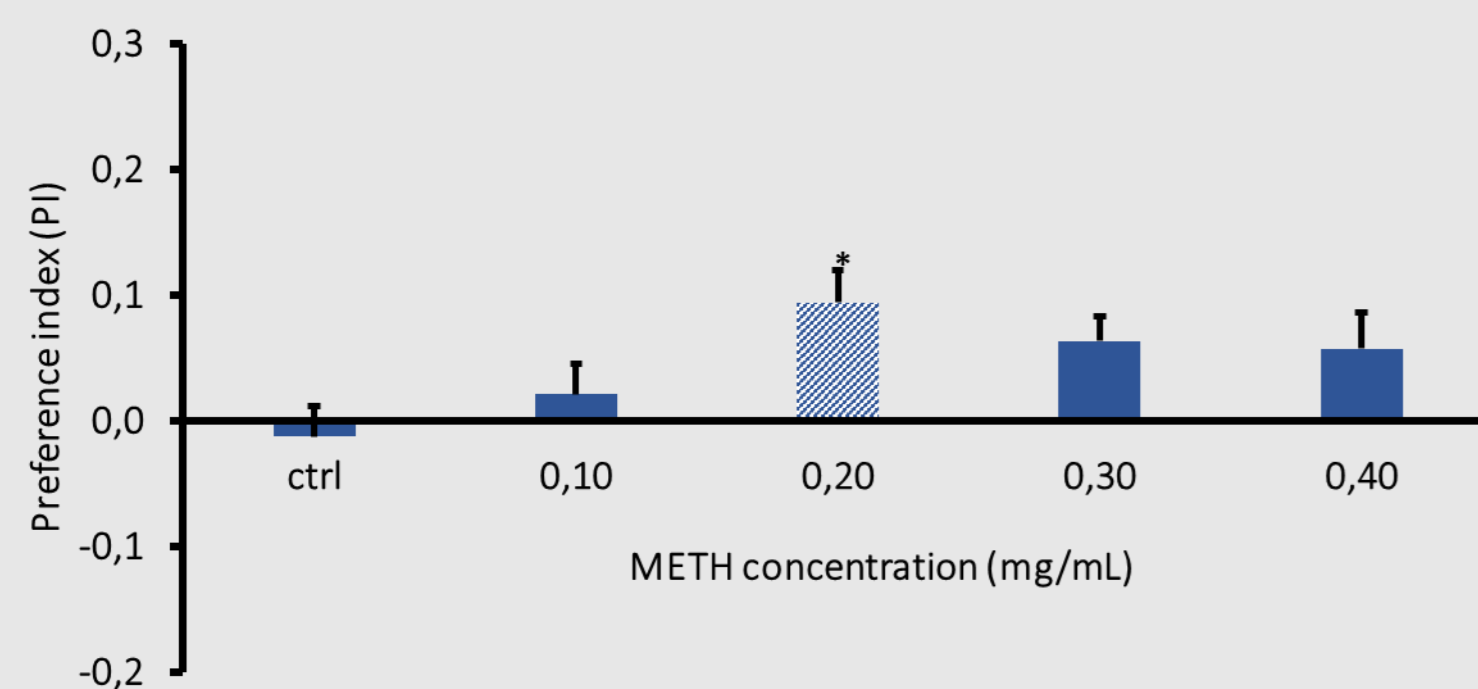
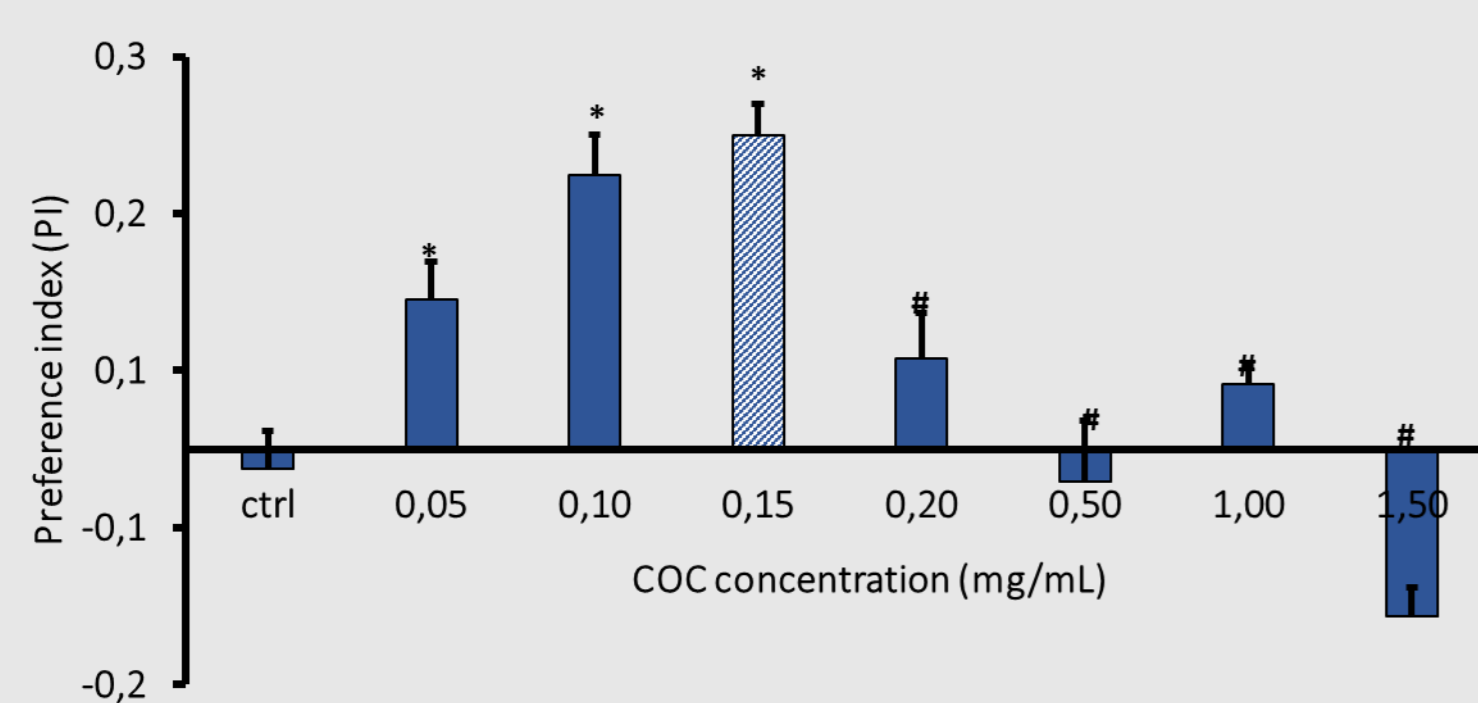
c) Mutants for:

- circadian genes *per⁰¹*, *tim⁰¹*, *clk^{Lrk}* and *cyc⁰¹*
- monoamine neurotransmission using *fmn*, *dumb* and *DDC-VMAT*

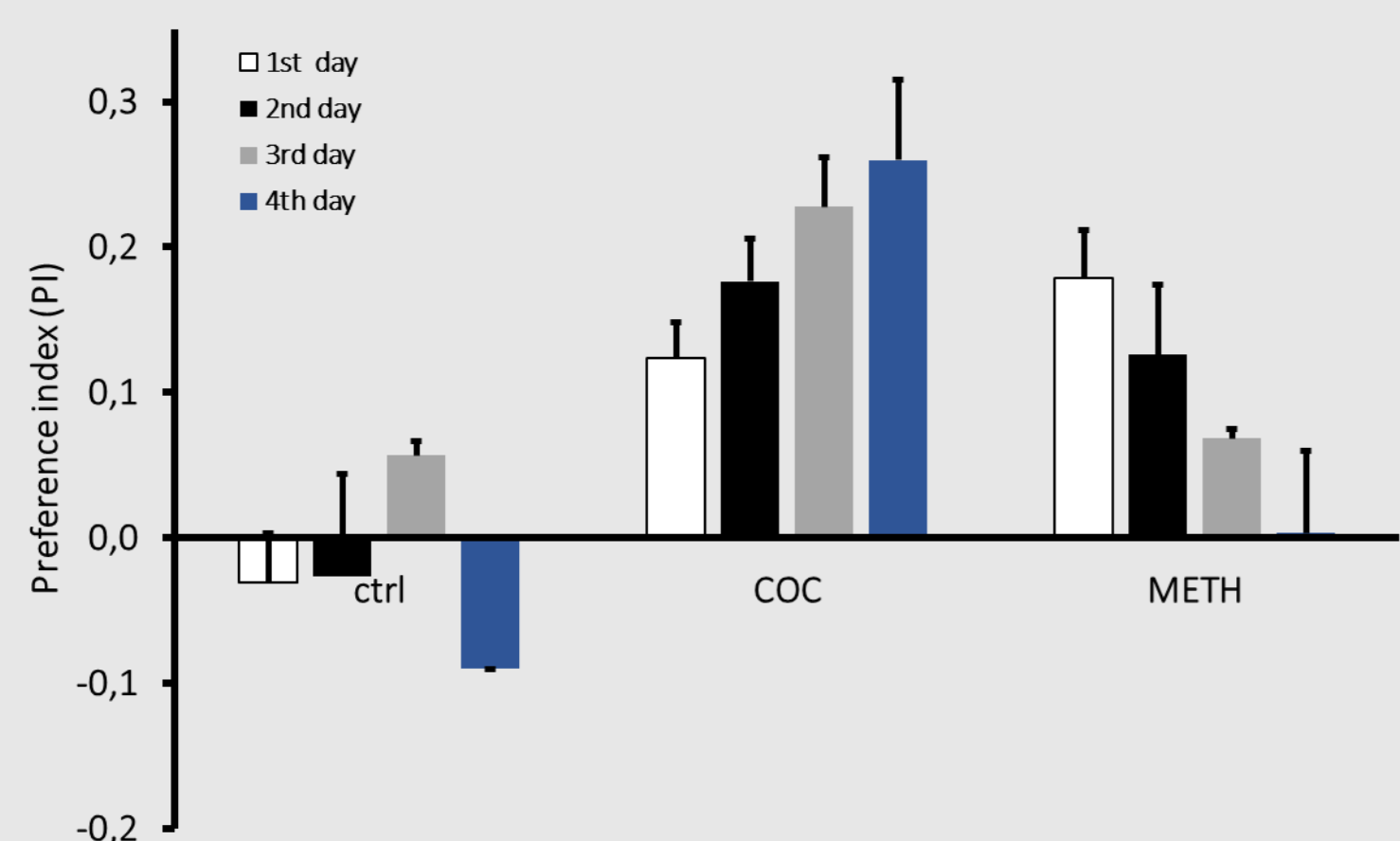
Results

Preferential consumption of COC and METH

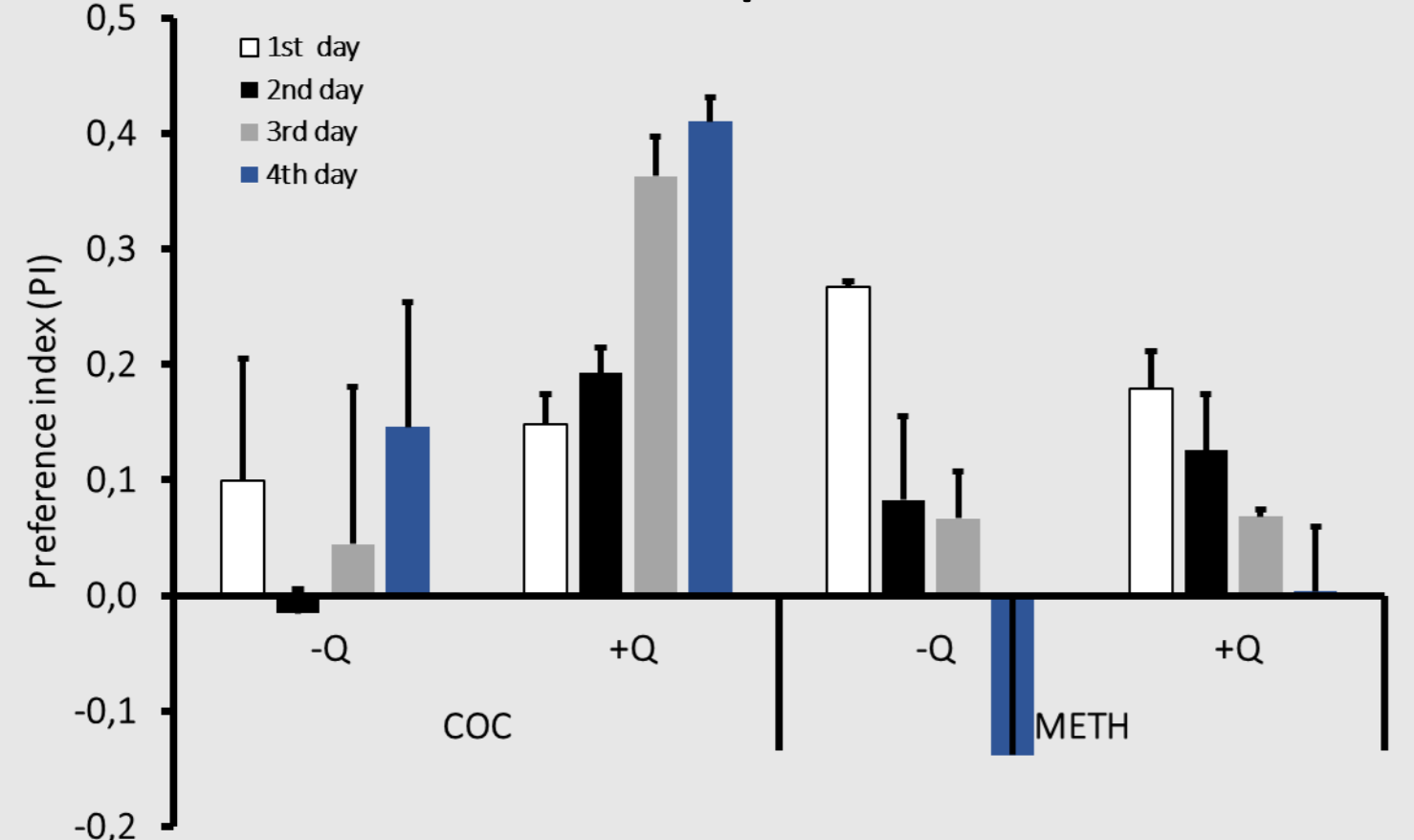
- *wt* flies preferentially and dose dependently consume COC and METH



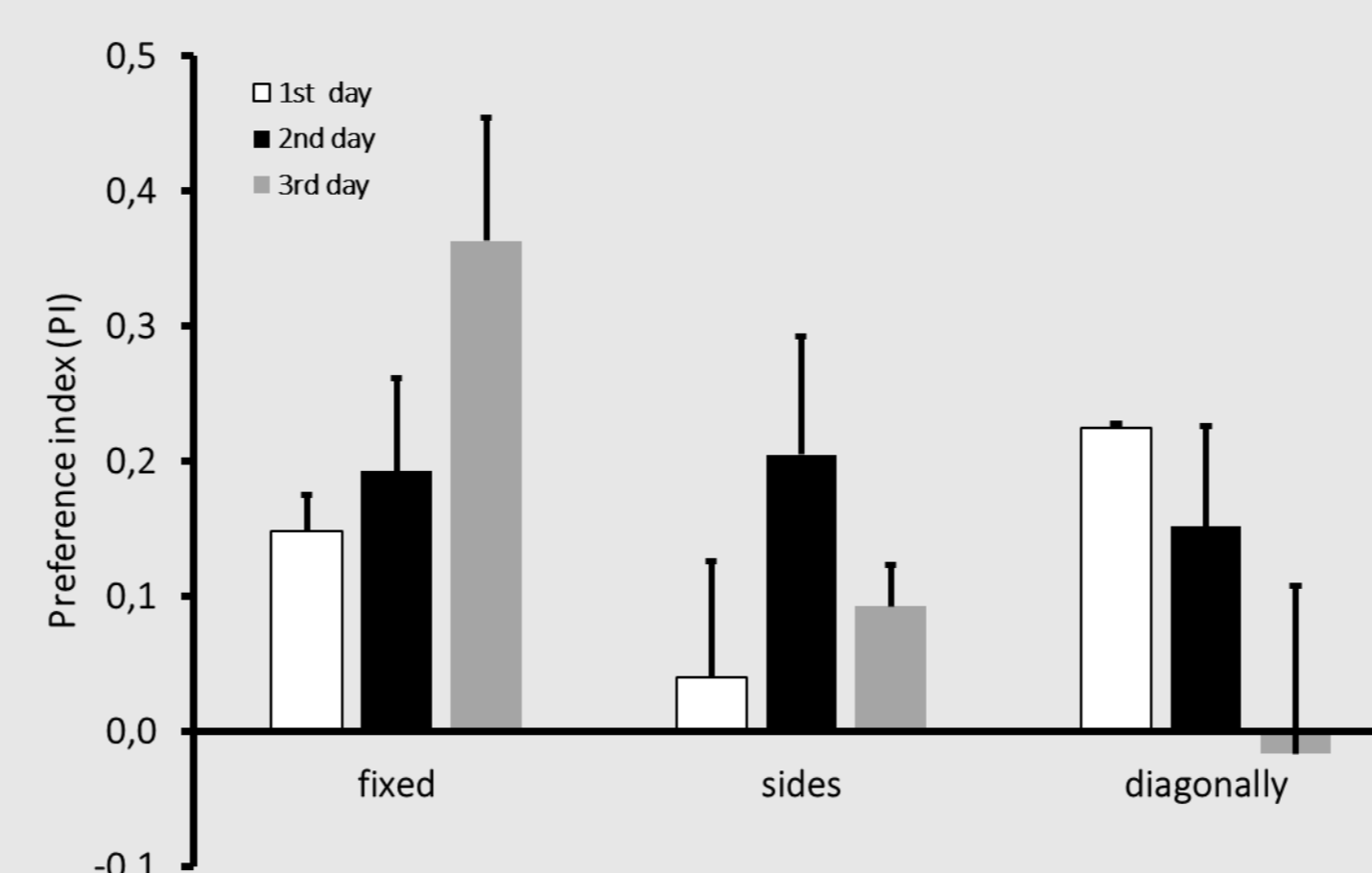
- preferential consumption of COC increases, while for METH decrease over several days



- preferential consumption of COC and METH is cue-dependent

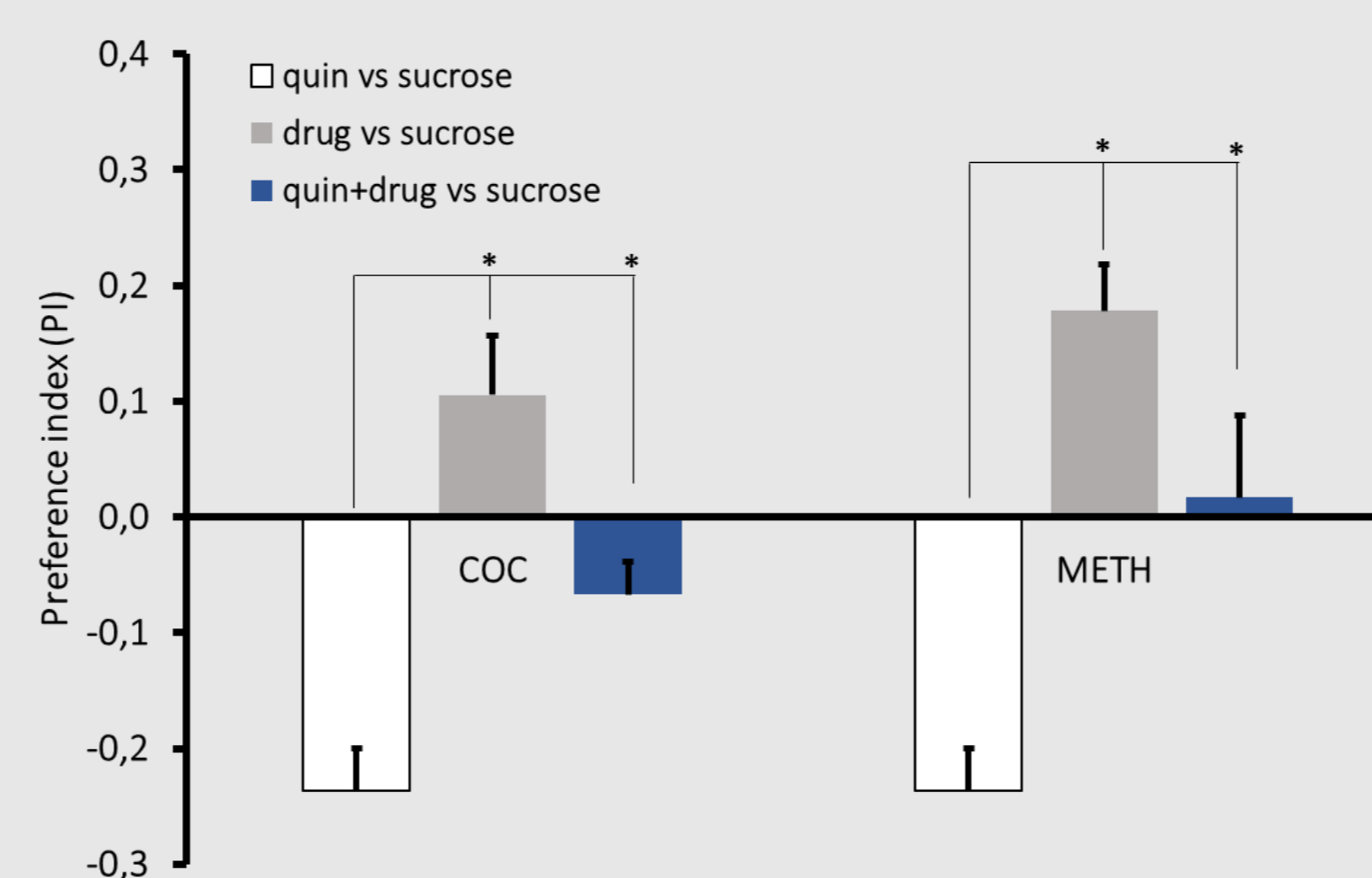


- preferential consumption of COC is greater with fixed location

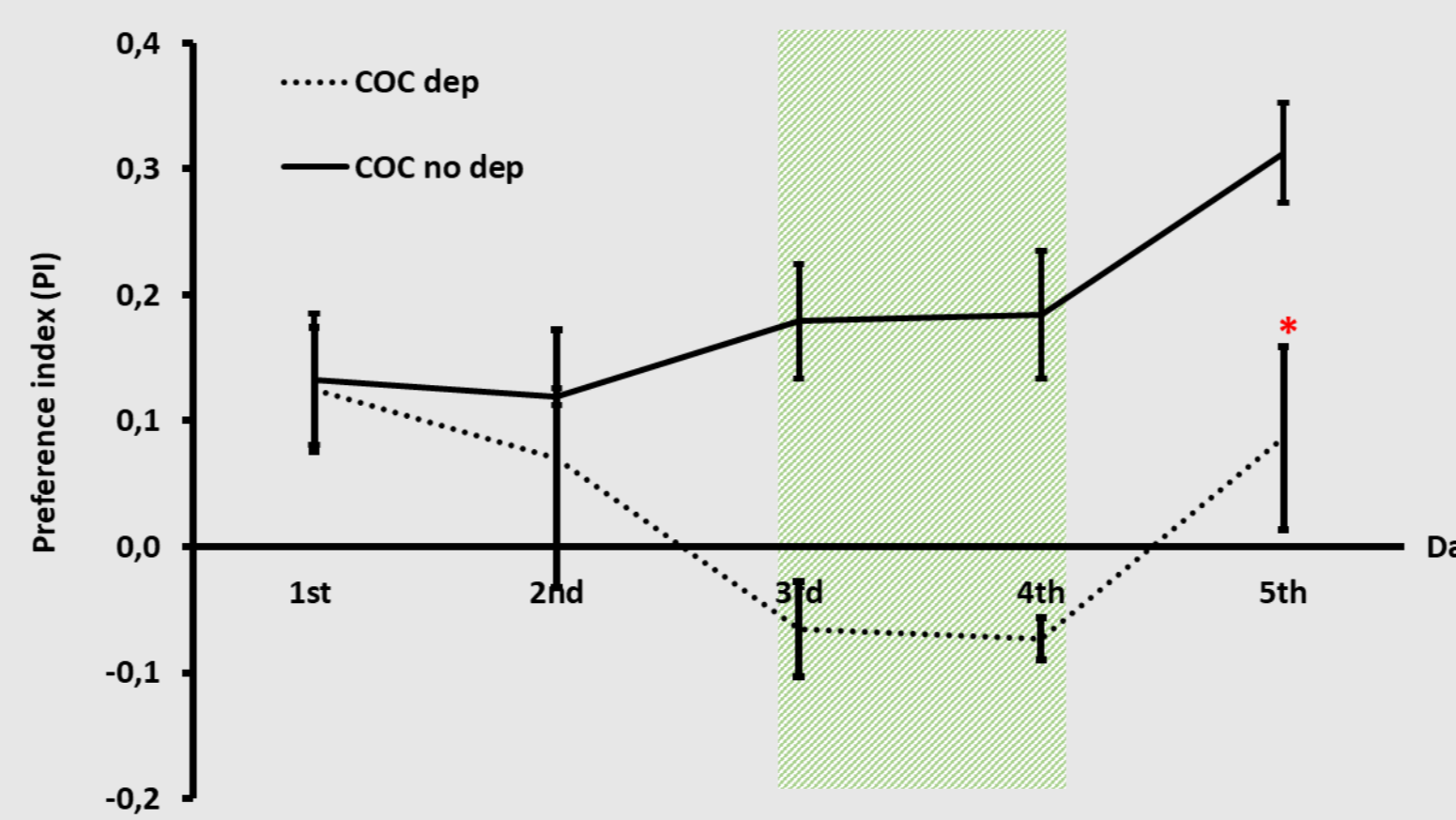


Flies develop features of addiction

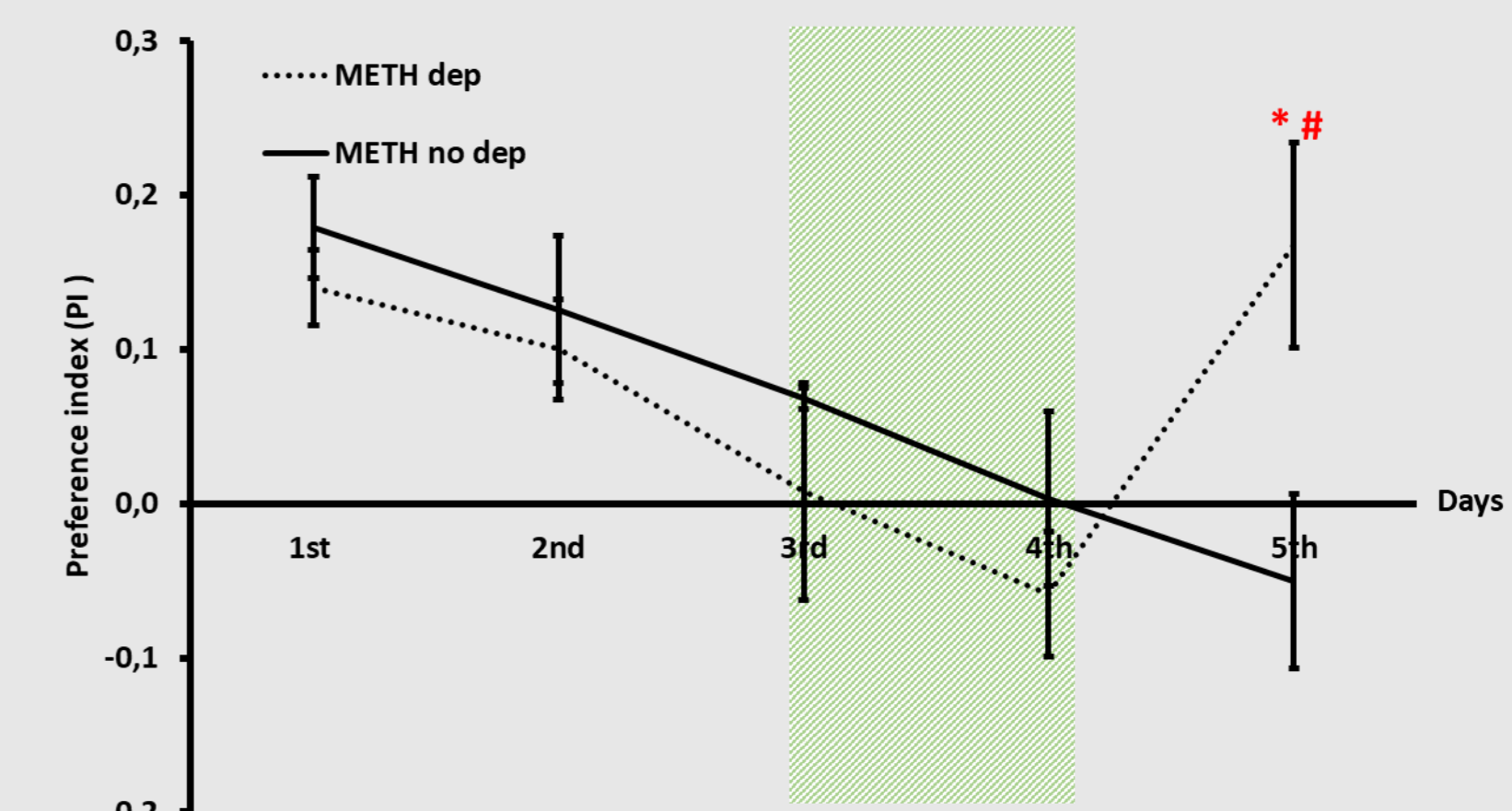
- preferential consumption of COC and METH in spite of added bitter taste



- same preferential consumption of COC after two days of deprivation

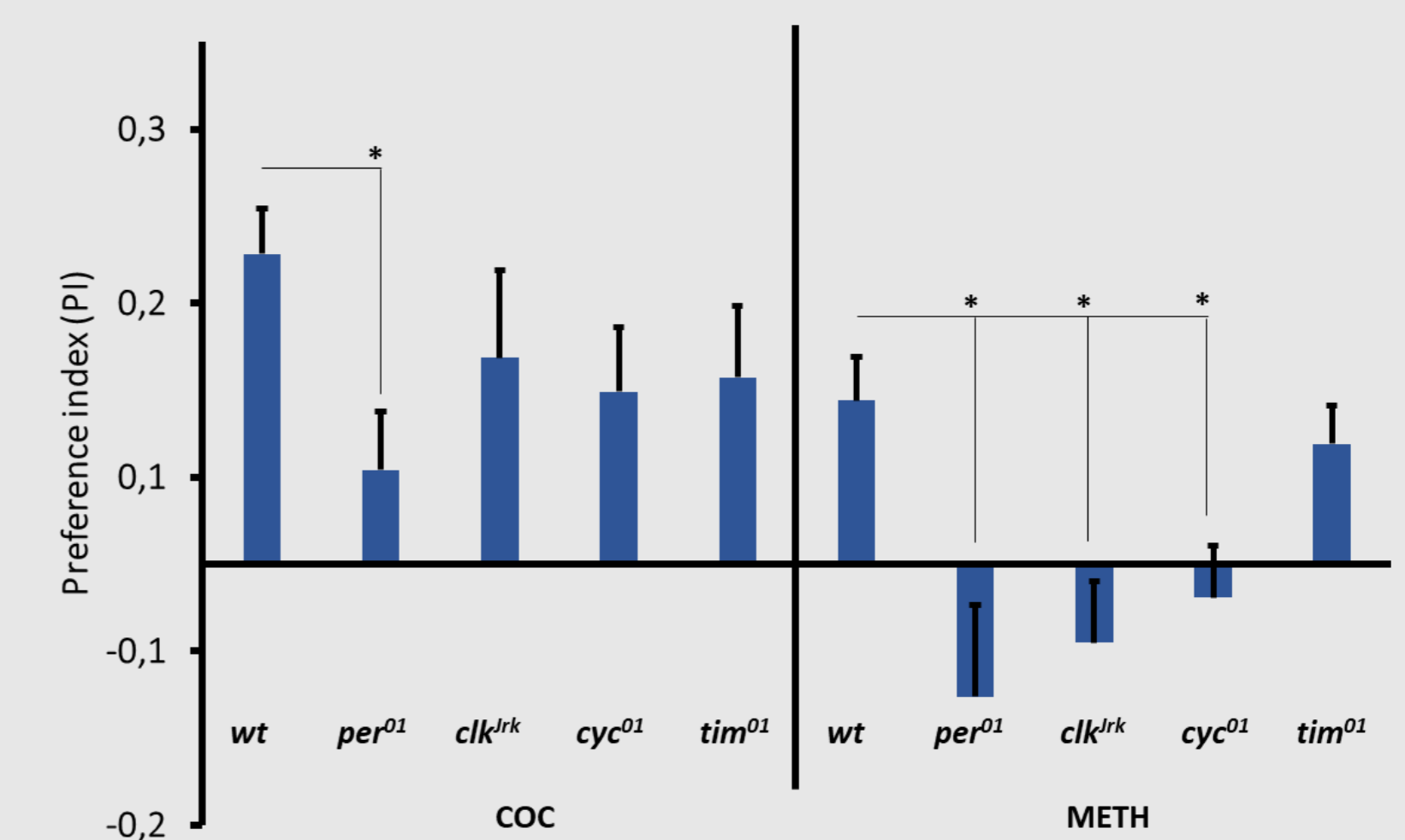


- greater preferential consumption of METH after two days of deprivation

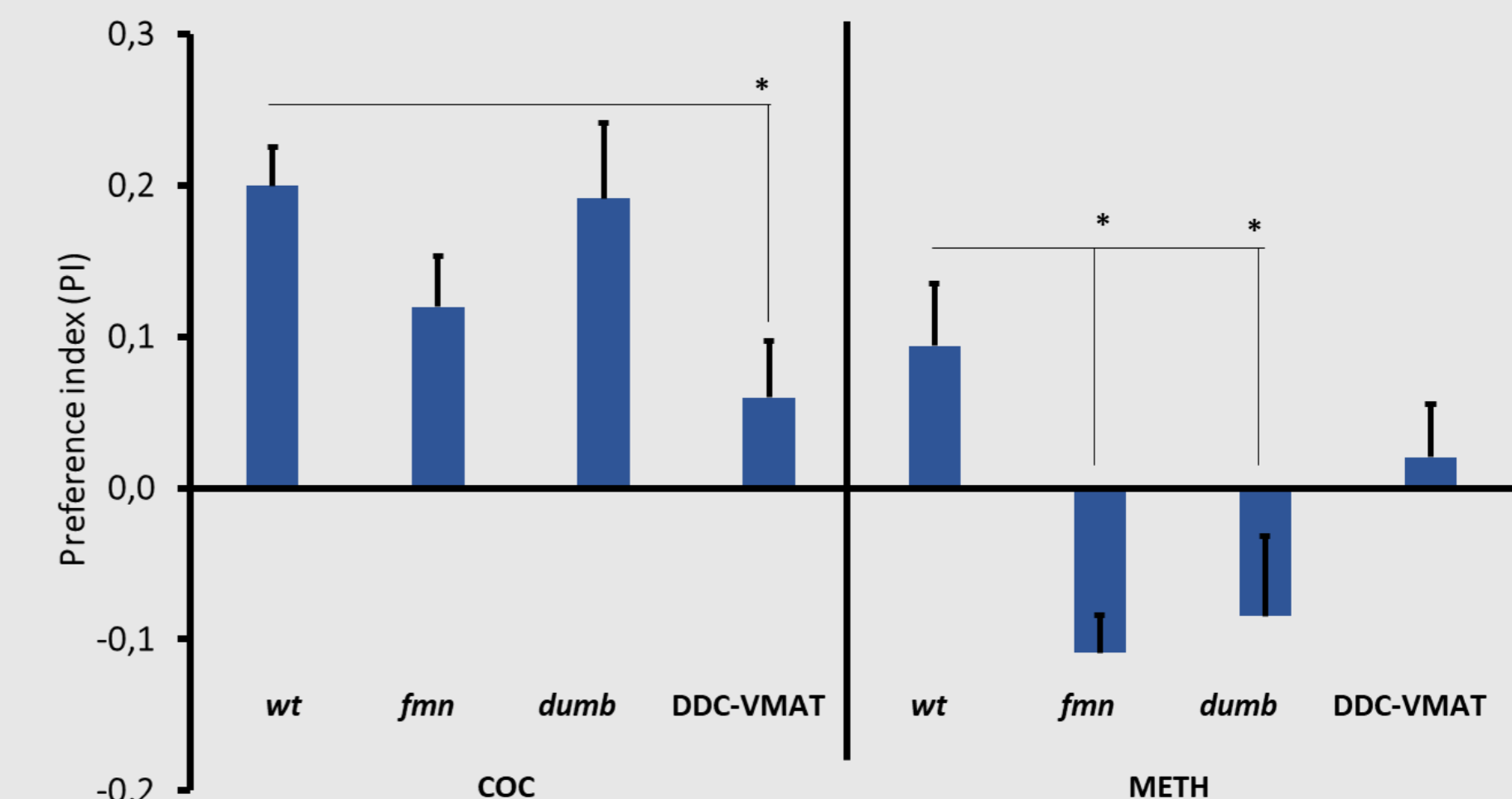


Genetic screen

- preferential consumption of METH depends on *per*, *Clk* and *cyc* gene, while for COC it depends on *per*



- preferential consumption of COC depends on VMAT in DDC neurons, and METH depends on DAT and DA1R



Conclusion

1. *Drosophila* shows difference in preferential consumption of COC and METH suggesting mechanistic difference of action on motivational circuits.
2. Dependence of preferential consumption on cue and location suggests inflexibility of behavior and/or involvement of mechanisms of learning and memory.
3. Flies overcome bitter taste of quinine to self-administer COC and METH.
4. Different circadian genes and components of monoaminergic signaling are involved in preferential consumption for COC and METH.
5. These data show that self-administration can be studied in *Drosophila*. COC and METH act on neuronal circuit controlling motivation for consumption of drugs. Neural mechanism underlying drug taking can be dissected in *Drosophila* using many genetic tools available in this model organism.