Embryonic exposure to amphetamine alters the activity of the dopamine transporter in adult animals and progeny

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Amphetamine (AMPH) is used as psychostimulant, appetite suppressant, performance enhancer and to treat Attention Deficit Hyperactive Disorder (ADHD). Despite its widespread use, the long-term consequences of this drug have been poorly investigated. Among other effects, AMPH has been shown to alter the function of proteins uniquely associated with the reward system, *i.e.* the dopamine transporter (DAT). Similarly to mammals, the nematode *Caenorhabditis elegans* (*C. elegans*) exhibits changes in behaviors when treated with AMPH, and we showed that these AMPH-induced behavioral changes are largely mediated by the *C. elegans* DAT (DAT-1). Here we investigated the behavioral and functional effects caused by chronic AMPH exposure during embryogenesis in *C. elegans* adults and progeny. We found that animals that were exposed to AMPH during embryogenesis exhibited higher values of AMPH-induced behaviors with respect to control animals. Interestingly, we found that the increased behavioral response, observed in the group of animals that received AMPH during embryogenesis, was inherited by the progeny. Because DAT-1 is one of the proteins required to generate AMPH-induced behaviors in both *C. elegans* and mammals, we tested whether embryonic exposure to AMPH alters the landscape of histone methylation associated with the promoter of the dat-1gene. Our ChIP experiments show that at the promoter of dat-1 of adult animals, embryonal AMPH exposure causes significant changes of specific histone markers associated with gene silencing. Interestingly, these same changes were observed also in progeny (F1 generation). Parallel experiments demonstrate that the ability of DAT-1 to reuptake dopamine was decreased in primary cultures of dopaminergic neurons (F1 generation) originated from animals exposed to AMPH during embryogenesis (F0 generation) with respect to control cultures. Taken together, these data suggest that chronic AMPH exposure during embryogenesis reduces expression of DAT in adult animals and this reduction in DAT expression is transmitted to progeny.

Because many of the components of the dopaminergic system as well as epigenetic mechanisms are highly conserved between *C. elegans* and mammals, these results could be critical for our understanding of how drugs of abuse initiate and promote addiction in adults and future generations.