Attenuated Vasodilation in Epinephrine-Deficient Mice: Impaired $\beta_2$ Response

It has been suggested that there is a link between epinephrine synthesis and the development of $\beta_2$-adrenoceptor–mediated effects. In this article, the study aim was to characterize $\beta_2$-adrenoceptor–mediated relaxation and facilitation of norepinephrine release in the aorta of phenylethanolamine-N-methyltransferase-knockout (Pnmt-KO) mice. Epinephrine is absent in Pnmt-KO mice. In isolated aortic ring studies, the potency and the maximal effect of the $\beta_2$-adrenoceptor agonist terbutaline were lower in Pnmt-KO than in wild-type (WT) mice. The selective $\beta_2$-adrenoceptor antagonist, ICI-118551 [(z-erythro-(S$^*$,S$^*$)-1-[2,3-(dihydro-7-methyl-1H-inden-4-yl)oxy]-3-[(1-methylethyl)amino]-2-butanol hydrochloride], antagonized the relaxation caused by terbutaline in WT mice, but not in Pnmt-KO mice. $\beta_2$-Adrenoceptor protein density was decreased in membrane aorta homogenates of Pnmt-KO mice, and this finding was supported by immunofluorescence confocal microscopy. In the absence of epinephrine, $\beta_2$-adrenoceptor protein density was decreased in aorta cell membranes, thus potentially hindering its functional activity.


Response to Ethanol in Adulthood Is Enhanced by Periadolescent Consumption

Alcohol drinking during adolescence is associated in adulthood with increased rate of alcohol dependence. In this article, experiments were designed to determine the effects of periadolescent alcohol drinking on the reinforcing properties of ethanol (EtOH) within the posterior ventral tegmental area (pVTA) and the ability of EtOH microinjected into the pVTA to stimulate dopamine release in the nucleus accumbens shell (AcbSh). The results indicate that rats that consumed EtOH during adolescence were more sensitive to its reinforcing effects (a lower concentration of EtOH supported self-administration), and the ability of EtOH microinjected into the pVTA to stimulate dopamine (DA) release in the AcbSh was enhanced. The data indicate that EtOH consumption during adolescence altered the mesolimbic DA system to be more sensitive and responsive to EtOH. This increase in the response to EtOH within the mesolimbic DA could be part of biologic sequelae that are the basis for the deleterious effects of adolescent alcohol consumption.

See article at J Pharmacol Exp Ther 2014, 351:317–326.

Factors Influencing Methamphetamine-Induced Neurovascular Change

Recently abstinent methamphetamine (Meth) abusers showed neurovascular dysregulation within the striatum. In this article, the study attempted to discover the factors contributing to dysregulation and why these effects persist. In rats, micro-computed tomography revealed a marked reduction in vessel diameter and vascular volume uniquely within the striatum between 1 and 28 days after Meth self-administration. Subsequently, it was determined that dopamine (DA) D2 receptors regulated Meth-induced striatal vasoconstriction, and that acute Meth exposure also increased striatal levels of endothelin receptor A and decreased neuronal nitric oxide synthase. Collectively, the data provide evidence that Meth-induced striatal neurovascular dysregulation involves DA receptor signaling that results in vasoconstriction via endothelin receptor A and nitric oxide signaling. As these effects can lead to hypoxia and trigger neuronal damage, these findings provide a mechanistic explanation for the selective striatal toxicity observed in the brains of Meth-abusing humans.

See article at J Pharmacol Exp Ther 2014, 351:432–439.

Chronic L-Dopa Decreases the Serotonin Neurons in the Dorsal Raphe Nucleus

Chronic L-dopa (L-3,4-dihydroxyphenylalanine) is administered to recover motor function in Parkinson’s patients. However, over time, debilitating side effects occur, such as dyskinesia and mood disturbances. Some of the side effects of L-dopa have been credited to its effect on serotonin (5-HT) neurons. In this article, the authors sought to determine whether chronic L-dopa treatment decreases 5-HT neurons in the DRN and 5-HT content in forebrain regions in an oxidative-stress–mediated manner. In rats treated with L-dopa for 10 days, the number of 5-HT neurons was significantly decreased in the dorsal raphe nucleus (DRN). This effect was more pronounced in the caudal extent of the dorsal DRN, a subregion found to have a significantly higher increase in the 3,4-dihydroxyphenylacetic acid/dopamine ratio in response to acute L-dopa treatment. Furthermore, pretreatment with ascorbic acid prevented the decreases in 5-HT neurons. In addition, 5-HT content was decreased significantly in the DRN and prefrontal cortex by L-dopa treatment, also preventing ascorbic acid pretreatment. Taken together, these data illustrate that chronic L-dopa causes a 5-HT neuron loss and the depletion of 5-HT content in a subregion of the DRN as well as in the frontal cortex through an oxidative-stress mechanism.