Exposure to standard cigarette smoke or electronic cigarette vapour induce short and long term behavioural alterations and a high sensitivity to low doses of Δ^9-Tetrahydrocannabinol

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Tobacco use continues to remain a serious public health problem and an urgent need persists for better drug therapies to treat nicotine dependence. In addiction the sales of e-cigarettes, as alternative smoking products, are becoming increasingly popular but until now only few studies are available on the effect of this device at the molecular and behavioural levels.
Recently, we have developed a new model of nicotine exposure which is able to induce nicotine dependence in male Balb/c mice exposed to conventional cigarette smoke or electronic cigarette vapour. Preliminary experiments, have been carried out exposing mice, in groups of 30, to a rodent ventilator delivering tobacco cigarette smoke (7 commercial cigarettes containing 0.8 mg of nicotine/cigarette, 10 mg of tar and 10 mg of carbon monoxide smoked) or e-cigarette vapour (containing 5.6 mg of nicotine dissolved in 1 ml of aqueous solution of propylene glycol (55%), glycerin (35%), flavor and fragrance agents) 3 times a day for 7 weeks. Control mice were exposed to the same ventilator using the same schedule but receiving only air.
A significant up-regulation of $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptor subtype in different brain areas of animals exposed to both e-cigarette and standard cigarette smoke, was found. Similar brain cotinine and nicotine concentrations increase and comparable urine cotinine levels were found. After mecamylamine-precipitated withdrawal there was a decrease in horizontal and vertical movements and the presence of typical withdrawal symptoms and signs in mice exposed to standard cigarette smoke which were more pronounced than those elicited by e-cigarette. A milder withdrawal syndrome was observed in animals exposed to e-cigarettes than to standard cigarettes. Spontaneous nicotine withdrawal syndrome evaluated starting from 24 hours up to 90 days after exposure revealed cognitive impairment and increased anxiety in both groups. Surprisingly, e-cigarette vapour exposure elicited early onset of depressive-like behaviour and a more severe compulsive behaviour, tested with marble burying task.
Marijuana smoking is prevalent in adolescent tobacco smokers (Rubistein et al., 2014). Notably, among adolescent tobacco smokers, who also smoke marijuana, the frequency of marijuana use was associated with greater levels of nicotine addiction. Thus, importantly, while no direct association between earlier onset of nicotine use and cannabis use disorders was found, earlier nicotine use may indeed be of indirect relevance for cannabis use disorder risk (Chen et al., 2005). So, we also tested whether 7 weeks of cigarette smoke or e-cigarette vapour exposure facilitated the subsequent reinforcing effects of Δ^9-Tetrahydrocannabinol (THC) after 2, 30 and 60 days from nicotine withdrawal, using Conditioned Place Preference task. Our preliminary results indicated that mice exposed to nicotine showed an higher sensitivity to lower doses of THC (0.01 mg/kg), compared to controls. The increased sensitivity to low doses of THC persists up to 30 days from nicotine withdrawal in animals previously exposed to the electronic cigarette and until at least 60 days in those exposed to conventional cigarettes.
In conclusion, our results show that standard tobacco cigarette and e-cigarette exposure induce short- and long- term effects. Our innovative nicotine exposure procedure in mice is also a valid model for nicotine addiction studies and for nicotine and other drugs of abuse interaction.

Rubinstein et al. (2014) *Drug and Alcohol Dependence* 141:159–162.
Chen et al. (2005) *Drug Alcohol Depend*. 79:11–22.