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The rewarding effects of ethanol are modulated by binge eating of a high-fat diet during adolescence

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ABSTRACT

Binge-eating is considered a specific form of overeating characterized by intermittent and high caloric food intake in a short period of time. Epidemiologic studies support a positive relation between the ingestion of fat and ethanol (EtOH), specifically among adolescent subjects.

The aim of this work was to clarify the role of the compulsive, limited and intermittent intake of a high-fat food during adolescence on the rewarding effects of EtOH. After binge-eating for 2 h, three days a week from postnatal day (PND) 29, the reinforcing effects of EtOH were tested with EtOH self-administration (SA), conditioned place preference (CPP) and ethanol locomotor sensitization procedures in young adult mice.

Animals in the high fat binge (HFB) group that underwent the EtOH SA procedure presented greater EtOH consumption and a higher motivation to obtain the drug. HFB mice also developed preference for the paired compartment in the CPP with a subthreshold dose of EtOH. Independently of the diet, mice developed EtOH-induced locomotor sensitization. After the SA procedure, HFB mice exhibited reduced levels of the mu opioid receptor (MOr) and increased cannabinoid 1 receptor (CB1r) gene expression in the nucleus accumbens (N Acc), and decreased of tyrosine hydroxylase (TH) gene expression in the ventral tegmental area (VTA).

Taken together the results suggest that bingeing on fat may represent a vulnerability factor to an escalation of EtOH consumption.

1. Introduction

Adolescence is a period of brain maturation during which individuals are especially vulnerable to environmental threats such as drug abuse or inadequate dietary habits (Cruz, 2000; Schneider, 2008; Bava and Tapert, 2010). Rates of overeating in the last years have grown, affecting mainly the young population (Herpertz-Dahlmann, 2015). Binge-eating is considered a specific form of overeating characterized by intermittent and excessive intake of caloric food in a short period of time (Davis et al., 2007). Many teenagers display this pattern of hedonic eating, which includes eating for pleasure, rather than for metabolic need, without reaching the clinical criteria for binge-eating disorder (Gold, 2011). Binge eating in animals is characterized by behavior patterns similar to those seen in humans. To be classified as a binge, animals must consume large quantities of food in a brief, defined period of time, and this quantity should exceed that consumed by control animals under similar circumstances, and must be stable and maintained over time (Corwin and Buda-Levin, 2004).

Results of epidemiologic studies support a bidirectional, positive relation between the ingestion of fat and ethanol (Swinburn et al., 1998; Stickley et al., 2015). Studies in animal models also support this relationship; rats chronically injected with EtOH

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exhibit increased fat preference (Barson et al., 2009), and fat-preferring rats consume more EtOH than water, a pattern that is not seen in carbohydrate-preferring rats (Krahn and Gosnell, 1991). Few studies were performed to elucidate if a high fat diet increases ethanol intake, and those that have been done reported discrepant results. A first report in the 70's found excessive ethanol drinking in rats fed a high-fat diet (Pekkanen et al., 1978). In a more recent study, Carrillo and co-workers (2004) demonstrated that daily overeating of fat over 7 days, a single high-fat meal, or the injection of fat could increase ethanol intake. However, Much et al. (2002) observed that different diets with varying protein and fat composition did not alter ethanol preference with the two-bottle choice.

Consumption of drugs of abuse and hedonic eating, besides sharing a high comorbidity, activates common DAergic pathways (Rada et al., 2005). Acute high-fat diet intake activates dopamine (DA) and the neural pathways involved in reward and motivation processes, (Valdivia et al., 2015). There is now compelling evidence that eating of highly palatable foods causes the same neuroadaptations as drugs of abuse (Grigson, 2002; Hajnal et al., 2008; Pelchat, 2002). In addition to DA, the opioid and endocannabinoid systems also play an important role in the reward process (Wang et al., 2004). Opioid signaling, especially the μ-opioid receptor, regulates the rewarding properties of palatable food, and alterations of this system have been identified in individuals with binge eating disorder (Cota et al., 2006). The endocannabinoid system is also crucial in appetite and reward regulation and modulates the dopamine and opioid systems (Cristino et al., 2014). It has been reported that a high fat diet upregulates endocannabinoid levels (Massa et al., 2010; Higuchi et al., 2012) and that CB1 antagonists reduce binge eating (Parylak et al., 2012).

Few studies have explored how binge eating modulates the intake of drugs of abuse. Binge-eating could act as a gateway for the development of drug addiction (Puhl et al., 2011), and an increase in the sensitivity of adult and adolescent rodents to the rewarding effects of psychostimulants after bingeing on fat has been described by our group and by others (Puhl et al., 2011; Blanco-Gandía et al., 2017). Although some reports suggest that fat intake increases preference for ethanol, a recent report by Sirohi et al. (2016) found that fat binge-fed rats displayed attenuated acquisition of alcohol intake in a preference choice paradigm. Therefore, there is a need to further evaluate the impact of high fat binging on the rewarding effects of ethanol. We have used the limited access model of Corwin et al. (1998), in which animals are allowed ad libitum access to standard food while having limited access to high fat food. The self-administration procedure (SA) has a high degree of validity, as it is a measure of motivation to consume the drug (Moeller and Stoops, 2015). In addition, we assessed vulnerability to the conditioned rewarding effects of EtOH to environmental cues using the Conditioned Place Preference (CPP) paradigm. The CPP is a very sensitive technique that can detect the rewarding effects of subthreshold doses of different drugs by assessing the vulnerability of animals to cue-related rewarding effects of the drugs (Tzschentke, 2007). Finally, given that it has been proposed that behavioral sensitization is linked to the hyperactivation of some of the cerebral pathways related to reward and addiction (Yamamoto et al., 2013), we also assessed locomotor sensitization to EtOH. At the end of the EtOH SA procedure, we also analyzed mu opioid receptor (MOr) and cannabinoid receptor (CB1r) gene-expression in the N Acc. Tyrosine hydroxylase (TH) gene expression was also determined in the VTA, a brain region of the dopaminergic mesolimbic pathway closely involved in the rewarding effects of alcohol consumption (Brodie et al., 1999).

2. Materials and methods

2.1. Subjects

115 male mice of the OF1 outbred strain were acquired commercially from Charles River (France). Animals were 21 days old on arrival at the laboratory and were all housed under standard conditions in groups of 6 (cage size 40 × 25 × 22 cm) for 4 days prior to initiating the experimental feeding condition at a constant temperature (21 ± 2 °C), with lights on from 8:00 to 20:00 h, and food and water available ad libitum (except during the behavioral tests).

All procedures involving mice and their care complied with national, regional and local laws and regulations, which are in accordance with Directive 2010/63/EU of the European Parliament and the council of September 22, 2010 on the protection of animals used for scientific purposes. The Animal Use and Care Committee of the University of Valencia approved the study.

2.2. Feeding conditions

Our feeding procedure is based on the limited access model described by Corwin et al. (1998), in which non-food-deprived animals with sporadic and limited access to a high-fat food develop binge-type behaviors. Two different types of diet were administered in the study. A standard diet (Teklad Global Diet 2014, 13 Kcal % fat, 67 Kcal % carbohydrates and 20% Kcal protein; 2,9 kcal/g; no sugars added) was given to the control group and a high-fat diet (TD.06415, 45 Kcal % fat, 36 Kcal % carbohydrates and 19% Kcal protein; 4,6 kcal/g; 20% of carbohydrates are sucrose) was administered in a limited way to the high-fat diet binge group. Both diets were supplied by Harlan Laboratories Models, S. L. (Barcelona, Spain) and will be referred to from now on as the standard diet and the high-fat diet, while the sporadic limited access to the high-fat food will be referred to as the high-fat diet binge (HFB).

On PND 25, mice were randomly divided into groups with similar average body weight (19–20 g) and assigned either a Control (C) diet or HFB (2 h access on Monday, Wednesday and Friday). All groups were fed the standard diet in their own cages 3 days a week and were exposed to a 2-h binge session in a different plastic cage (standard diet for the control group and high-fat diet for the HFB groups). Water was freely available at all times. Binge sessions took place 2–3 h after initiation of the dark phase. Animals were weighed every Monday, Wednesday and Friday throughout the study, at which point their intake of standard diet in their home cage was measured.

An overall description of the experimental procedure with a detailed description of the experimental procedure of the oral EtOH self-administration is provided in Table 1.

2.3. Drugs

For the oral self-administration procedure, absolute ethanol (Merck, Madrid, Spain) was dissolved in water using a w/v percentage, i.e. a 6% (w/v) ethanol solution equivalent to a 7.6% (v/v) ethanol solution. Saccharin sodium salt (Sigma, Madrid, Spain) was diluted in water. For the CPP and locomotor activity experiments, ethanol (Scharlab S.L., Barcelona, Spain; EtOH), obtained from an initial stock of a 96% v/v solution was diluted at a concentration of 20% v/v in physiological saline (NaCl 0.9% w/v; Sal) and injected intraperitoneally (IP) at a dose of 0.75 (CPP) and 2 g/kg locomotor activity. Control mice were injected IP with the corresponding volume of Sal.