European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro

Maternal separation increases alcohol-drinking behaviour and reduces endocannabinoid levels in the mouse striatum and prefrontal cortex

Marta Portero-Tresserra[a], Irene Gracia-Rubio[a], Lídia Cantacorps[a], Oscar J. Pozo[b], Alejandro Gómez-Gómez[b], Antoni Pastor[b], Raúl López-Arnau[c], Rafael de la Torre[b], Olga Valverde[a,d,*]

[a]*Neurobiology of Behaviour Research Group (GReNeC-NeuroBio), Universitat Pompeu Fabra, Barcelona, Spain*
[b]*IMIM-Hospital del Mar Medical Research Institute. Integrative Pharmacology and Systems Neuroscience Research Group, Barcelona, Spain*
[c]*Department of Pharmacology, Toxicology and Medicinal Chemistry, University of Barcelona, Barcelona, Spain*
[d]*Neuroscience Research Program, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain*

Received 24 August 2017; received in revised form 4 December 2017; accepted 7 February 2018

KEYWORDS
Alcohol;
Maternal separation;
Adolescence;
Endocannabinoids;
Monoamines;
Striatum

Abstract
Childhood adversity is associated with an increased risk of mood, anxiety and substance use disorders. Maternal separation is a reliable rodent model of early life adversity that leads to depression-like symptoms, which may increase the vulnerability to alcohol consumption during adolescence. However, the specific alterations in the pattern of alcohol consumption induced by maternal separation and the underlying molecular mechanisms are still unclear. The purpose of this study is to evaluate the long-term effects of maternal separation with early weaning (MSEW) on emotional and social behaviour, alcohol rewarding properties, and alcohol consumption, abstinence and relapse in adolescent male C57BL/6 mice. In addition,

Abbreviations: 2-AG, 2-arachidonoylglycerol; 2-LG, 2-linoleoylglycerol; 2-OG, 2-oleoylglycerol; 5-HIAA, 5-hydroxyindoleacetic acid; AEA, N-arachidonoylethanolamine; BAC, Blood Alcohol Concentration; CPP, Conditioned Place Preference; DEA, N-docosatetraenoylethanolamine; DHEA, N-docosahexaenoylethanolamine; DID, Drinking in the Dark; DOC, Deoxycorticosterone; EC, Endocannabinoid; EPM, Elevated Plus Maze; EtOH, Alcohol; LC-MS/MS, Liquid Chromatography-Tandem Mass Spectrometry; LEA, N-linoleoylethanolamine; MSEW, Maternal Separation with Early Weaning; NAE, N-acylethanolamide; OEA, N-oleoyl ethanolamide; PEA, N-palmitoylethanolamine; POEA, N-palmitoleoylethanolamine; PD, Postnatal Day; PFC, Prefrontal Cortex; SEA, N-stearoylethanolamine; SN, Standard Nesting; Trp, Tryptophan; TST, Tail Suspension Test; Tyr, Tyrosine

*Corresponding author at: Neurobiology of Behaviour Research Group (GReNeC-NeuroBio) Department of Experimental and Health Sciences Universitat Pompeu Fabra, C/ Dr. Aiguader, 8808003 Barcelona, Spain.
E-mail address: olga.valverde@upf.edu (O. Valverde).

https://doi.org/10.1016/j.euroneuro.2018.02.003

endocannabinoid and monoamine levels were analysed in discrete brain areas. Results showed that MSEW mice presented emotional alterations related to depressive-like behaviour and modified endocannabinoid levels in the striatum and the prefrontal cortex. MSEW mice also showed impairments in alcohol-induced conditioned place preference and higher alcohol intake in a model of binge drinking. Moreover, MSEW animals displayed a higher propensity to relapse in the two-bottle choice paradigm following a period of alcohol abstinence associated with reduced monoamine levels in the striatum. Such results indicate that exposure to early life stress increased the vulnerability to alcohol binge-drinking during adolescence, which may be partially explained by decreased sensitivity to alcohol rewarding properties and the ability to potentiate alcohol intake following a period of abstinence.

1. Introduction

Early postnatal life is a period of high vulnerability in which prolonged exposure stressors may lead to long-lasting deleterious effects on brain neurodevelopment and function. Therefore, preclinical (Kaufman et al., 2000; Sarro et al., 2014) and clinical studies (Lupien et al., 2009; Teicher and Samson, 2013) suggest that early life events exert a sustained influence over neural systems mediating stress reactivity. Maternal separation is a validated rodent model of early life stress frequently used to replicate early adversities, entailing the early separation of pups from dams for long periods after birth (Tractenberg et al., 2016). Previous studies have shown that maternal separation affects the formation of neuronal networks and exerts long-lasting effects on neural function (Nishi et al., 2014). Moreover, maternal separation leads to high levels of anxiety-like behaviour and high stress hormone responsiveness, depression-like behaviour assessed as anhedonia, despair behaviour and a decrease in behavioural responses to novelty (George et al., 2010; Gracia-Rubio et al., 2016a; Lukkes et al., 2017; Matthews and Robbins, 2003; Rüedi-Bettschen et al., 2004). In addition, maternal separation decreases neurogenesis (Lajud et al., 2012), reduces 5-HT1A receptor levels (Bravo et al., 2014; Gracia-Rubio et al., 2016b), and increases pro-inflammatory cytokines levels in serum (Réus et al., 2015) associated with increased neuroinflammatory responses (Gracia-Rubio et al., 2016a). Behavior and molecular alterations induced by maternal separation appear during adolescence and persist until adulthood (Gracia-Rubio et al., 2016a).

In this sense, adolescence is a critical period for brain development and maturation and is a sensitive period to develop psychiatric illnesses, including anxiety, mood and substance abuse disorders (Paus et al., 2008). The earlier drug use is initiated, the more likely it is for addiction to progress (Degenhardt et al., 2008) and at the same time, risk taking and novelty seeking are hallmarks of typical adolescent behaviour (Wolf et al., 2013). Alcohol is the most commonly abused drug during adolescence and alcohol intoxication was reported to induce brain damage (Pascual et al., 2014). Therefore, alcohol intake during adolescence is considered one of the main risk factors contributing to the development of neuropsychiatric disorders later in life (Skogen et al., 2014), including alcohol use disorder (Kyzar et al., 2016). Additionally, the individual risk of developing alcohol use disorder is affected by early life stress (Sinha, 2008), suggesting that the dysregulation of the brain reward function induced by early life adverse experiences may be related to the development of drug addiction (Cheetham et al., 2010), presumably through the modulation of the dopaminergic and endocannabinoid (EC) systems (Parsons and Hurd, 2015), which are involved in reward, mood and stress processing. Accordingly, previous reports showed that maternally separated animals present a lower density of dopamine transporter sites in the striatum, greatly reduced D2 (Gracia-Rubio et al., 2016b) and D3 dopamine receptor binding (Brake et al., 2004). Moreover, regarding the EC system, a decreased CB1 receptor expression was described in the hippocampus and prefrontal cortex (PFC) due to maternal separation, while in the striatum, an increase was reported (López-Gallardo et al., 2012; Romano-López et al., 2012), which may contribute to a proclivity to alcohol ingestion (Parsons and Hurd, 2015). Several studies have concluded that animals exposed to maternal separation exhibit high patterns of alcohol consumption (García-Gutiérrez et al., 2016; Gondré-Lewis et al., 2016; Roman and Nylander, 2005) during adulthood. Nevertheless, only a few studies have evaluated the effects of maternal separation on alcohol consumption during adolescence (García-Gutiérrez et al., 2016), and previous literature has not investigated the effects of maternal separation during alcohol abstinence and relapse.

It is, therefore, of interest to understand the underlying neurobiological mechanisms by which early life stress may contribute to the vulnerability to develop alcohol use disorders during adolescence, specially the contribution of the EC and the monoaminergic systems as related key targets in the abuse liability of alcohol. In this context, the aim of the present study was first to examine whether maternal separation may increase the propensity to alcohol consumption, and second to determine if it modifies the EC and the monoaminergic systems in the PFC and striatum in adolescent male C57BL/6 mice. For this purpose, to verify the effects of maternal separation on despair-like and social behaviour, the tail suspension test (TST) and the three-chamber social test were assessed respectively. Moreover, to evaluate the effects of maternal separation on alcohol rewarding properties, voluntary alcohol intake, binge

Please cite this article as: Portero-Tresserra, M., et al., Maternal separation increases alcohol-drinking behaviour and reduces endocannabinoid levels in the.... European Neuropsychopharmacology (2018), https://doi.org/10.1016/j.euroneuro.2018.02.003