SCH Salud y Conducta Humana

Abstract

PHSU PONCE HEALTH SCIENCES UNIVERSITY · School of Behavioral · and Brain Sciences

FAAH Inhibition with URB-597 Mitigates Neuroinflammation-Associated Deficits in Working and Recognition Memory in Male Rats

Héctor A. López-Rivera, Alfredo Frontera, Ema Abreu, Gerardo Rosa, Camen Maldonado-Vlaar

Universidad del Sagrado Corazón, San Juan, PR

University of Puerto Rico, Rio Piedras, San Juan, PR

ABSTRACT

Introduction. Neuroinflammation contributes to cognitive decline by impairing learning, memory, and synaptic plasticity. Systemic lipopolysaccharide (LPS) is widely used to model inflammation-associated behavioral and cognitive changes. The endocannabinoid system (ECS) modulates stress responses, synaptic signaling, and neuroimmune function. Inhibiting fatty acid amide hydrolase (FAAH) with URB-597 increases anandamide (AEA) availability and may attenuate inflammatory effects; however, its impact on LPS-induced cognitive deficits remains unclear. **Objective.** To determine whether FAAH inhibition with URB-597 modulates the behavioral and cognitive consequences of LPS-induced neuroinflammation in male rats. **Method.** Male Sprague-Dawley rats (n = 25) were assigned to Control (saline), URB-597, LPS, or LPS + URB-597 groups across a 23-day protocol comprising habituation, baseline testing, and short- and long-term treatment phases, each followed by behavioral testing. Recognition memory was assessed with the Novel Object Recognition (NOR) task and working memory with spontaneous alternation in the T-maze. Behavior was scored with conventional methods and automated behavioral phenotyping. **Results.** In short-term NOR testing, discrimination indices were variable and showed no consistent group-dependent pattern. In long-term T-maze testing, LPS-treated animals showed lower spontaneous alternation than controls (44% vs. 81%), whereas LPS + URB-597 animals showed intermediate performance (51%). LPS was also associated with locomotor alterations that may partially confound memory outcomes. **Conclusions.** These findings suggest that LPS impairs long-term spatial working memory and that FAAH inhibition with URB-597 produces partial behavioral recovery, consistent with a modulatory rather than fully restorative effect. Recognition memory showed no clear novelty preference across groups. Future studies will confirm target engagement (FAAH activity and AEA levels), examine inflammatory biomarkers and CB1/CB2 receptor involvement, and assess sex-dependent effects.

Keywords: FAAH; URB-597; anandamide; endocannabinoid system; neuroinflammation; lipopolysaccharide; working memory; recognition memory; Sprague-Dawley rat