8TH INTERNATIONAL CONGRESS
53ª JORNADAS NACIONALES
SEVILLA 15/17 OCTUBRE 2026
SOCIDROGALCOHOL
Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

Sex-specific peripheral regulation of plasma Apo J and Apo M following alcohol binge drinking-induced peripheral oxidative stress

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Introduction

Binge drinking (BD) is a heavy pattern of alcohol consumption known to cause severe oxidative stress, widespread peripheral inflammation, neuroinflammation and related cognitive deficits.

Apolipoproteins (Apo) J and M are high density lipoproteins (HDL) components that participates in endotoxic clearance mechanisms, lipid metabolism and protect against inflammation and oxidative stress[1].

BD-induced oxidative stress can modify lipoprotein to form **oxidised high density lipoprotein (oxHDL)**, which may exacerbate neural damage due to its proinflammatory properties.

Thus, **dysregulation of these apos and the accumulation of oxHDL could potentially mediate alcohol binge-induced inflammation and its consequences.**

Objetive

Characterize sex-specific differences in alcohol binge-induced expression of peripheral and central ApoJ, ApoM and oxHDL, as possible regulators of the oxidative stress and neuroinflammation.

Method

Animals: 26 Young adults male (n=13) and female (n=13) Wistar rats, divided into two experimental groups: *control* (n= 12) and *EtOH* (n=14).

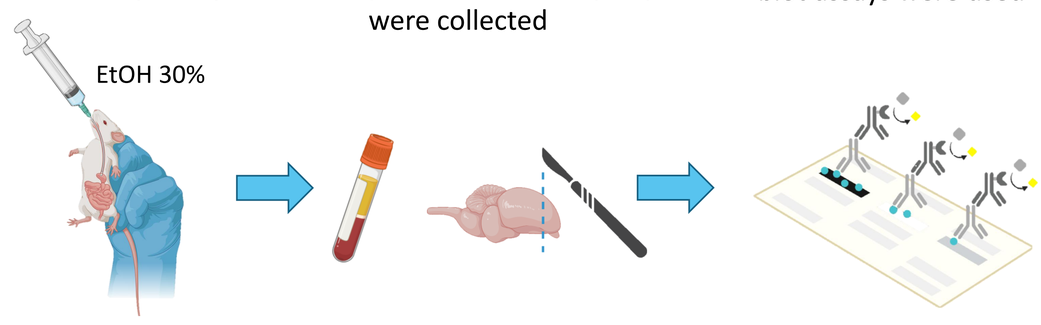
Table 1. Experimental Schedule: intragastric (i.g) alcohol 30% administration, 3 times per day, for 4 days, following Majchrowick binge drinking model[2].

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5
30% EtOH i.g 15:00h / 23:00h	30% EtOH i.g 7:00h /15:00h / 23:00h	30% EtOH i.g 7:00h /15:00h / 23:00h	30% EtOH i.g 7:00h /15:00h / 23:00h	30% EtOH i.g 7:00h Samples collect

Administration: Intragastric (i.g.) via, 3 times/day/4 days

Samples: Last day plasma and prefrontal cortex (PFC) were collected

Protein analysis: ELISA and western blot assays were used



Results

Table 2. Blood ethanol levels (BELs) and acumulative alcohol doses *per day*.

	MALES		FEMALES		t-test
	Control	EtOH	Control	EtOH	
BELs (mg/dL)	-------	280.1 ± 38.39	------	212.7 ± 35.01	p = 0.2188 n.s
Accumulative doses (g/kg/day)	-------	9.429 ± 0.1867	-------	10.43 ± 0.3120	*p = 0.0176

Table 2. Plasma ethanol (EtOH) concentration (mg/dL) on female and male young adult rats after the sacrifice and **accumulative doses *per day*** for each group after 96-hours of experiment (12 doses total, g/kg/day).

Both sexes showed **blood ethanol levels (BELs) above 80 mg/dL** considered as binge following this protocol. Additionally, **females appear to require larger amount of alcohol** to achive signs of intoxication comparable to those observed in males.

*Data are expressed as mean ± S.E.M. Statistical analysis by Student's t-test: *p < 0.05, n.s.: non-significant.*

Figure 1. Plasma levels of Apos and oxHDL

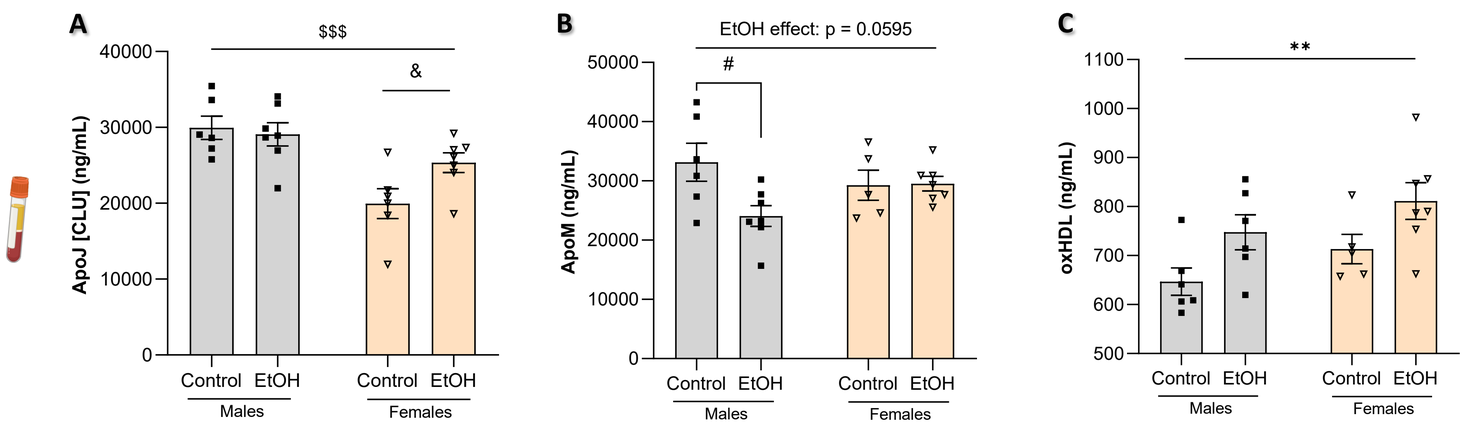


Figure 1. (A) Plasma ApoJ concentrations (ng/mL); **(B)** Plasma levels of ApoM (ng/mL); and **(C)** Plasma levels of oxidized HDL (oxHDL, ng/mL) across experimental groups, as determined by commercial ELISA kits.

Alcohol exposure produced an **upregulation of plasma ApoJ** levels in **females**, but not in males; while showed a **downregulation of ApoM** levels in **males**, without effect in females. Regarding oxHDL, **BD significantly increased oxidative stress in plasma in both sexes**.

*Data are expressed as mean ± S.E.M. Statistical analysis by 2-way ANOVA: overall ethanol effect: **p < 0.01; overall sex effect: $$$p < 0.001; and interaction effect (p = 0.0461): Bonferroni's post hoc #p < 0.05. A subsequent Student's t-test (&p < 0.05) showed an ethanol effect only in females in oxHDL levels.*

Figure 2. Prefrontal cortex (PFC) levels of Apos, oxHDL and TLR-4.

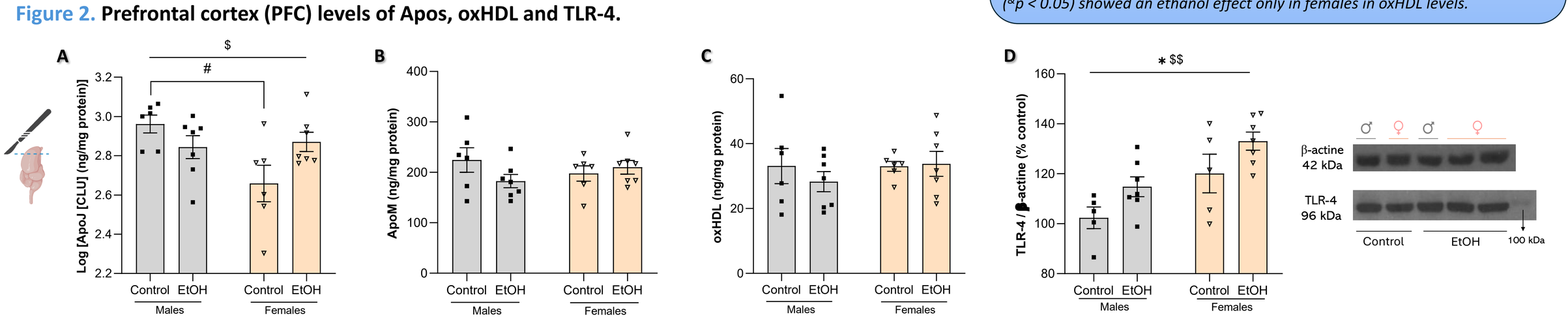


Figure 2. (A) Log-transformed ApoJ levels (ng/mg total protein); **(B)** ApoM levels (ng/mg total protein); **(C)** Cortical oxHDL levels (ng/mg total protein) across experimental groups, as determined by commercial ELISA kits. **(D)** TLR-4 protein expression levels expressed as a percentage of control (β-actine normalized) quantified by Western Blot.

This alcohol exposure paradigm triggers a **neuroinflammatory response**, as evidenced by the **upregulation of innate immune Toll-like receptor 4 (TLR-4) in both males and females**. Meanwhile, **ApoJ exhibits sex-specific differences under baseline conditions**, characterized by lower levels in females. However, this protocol of **BD produced no significant alteration in brain apolipoprotein expression.**

*Data are expressed as mean ± S.E.M. Statistical analysis by 2-way ANOVA: overall ethanol effect: *p < 0.05; overall sex effect: $$p < 0.01; interaction between factors (alcohol/sex), followed by Tukey's post hoc test: #p < 0.05.*

Conclusion

Alcohol abuse induces a **sex-specific peripheral homeostatic** response after BD, with differences in the expression of **ApoJ and ApoM** to counteract oxidative stress.

The expression of these **apolipoproteins showed alterations in plasma but not in the PFC under this protocol**.

Consequently, further investigations are required to elucidate the implication of ApoJ and ApoM in the pathophysiology of alcohol abuse.

References

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Fundings

This study has been supported by FEDER and the Spanish Ministry of Science, Innovation and Universities (ref: PID2021-127256OB-I00 and PID2025-171489OB-I00 to LO) and ISCIII Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS): Red de Investigación en Atención Primaria de Adicciones (RIAPAd; grant RD24/0003/0010; IP: LO) co-founded by the European Union (Fondo Europeo de Desarrollo Regional FEDER).