Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue1abst007.pdf

Neonatal Maternal Deprivation And A High Fat Diet Induce Sex-Dependent Effects On Endocannabinoid Levels In Three Different Types Of Adipose Tissues

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Maternal deprivation (MD) during neonatal life has diverse long-term effects, including modification of metabolism. We have previously reported that MD modifies the metabolic response to high fat diet (HFD) intake, with this response being different between males and females. In turn, previous studies also indicate that in mice made obese with HFDs endocannabinoid levels are deeply altered in various brown and white adipose tissue depots.

In this study, we analyzed the effects of MD (24h at postnatal day 9), alone or in combination with a HFD from weaning until the end of the experiment in Wistar rats of both sexes (Mela V et al, PLoS ONE 7:e48915, 2012). Brown adipose, peri-renal and subcutaneous adipose tissues were collected and the levels of anandamide (AEA), 2-arachidonoylglycerol (2-AG), palmitoyl-ethanolamide (PEA) and oleoyl-ethanolamide (OEA) were determined (Matias I et al, J Clin Endocrinol Metab 91:3171, 2008). Post-hoc comparisons (Tukey test) performed after three- and two-way ANOVAs were realised over the collected results.

Results: Brown adipose tissue: No significant effects of MD or HFD were found for AEA or 2-AG and, for this latter endocannabinoid, a marked sexual dimorphism was found among control animals with females showing significantly higher values than males (0.68 ± 0.07 pmol/mg vs 1.49 ± 0.18 pmol/mg; $p<0.05$). MD increased PEA levels in animals fed with control diet ($F_{1,27}=8.45$; $p<0.01$) but not in the animals under HFD. Besides, in females (but not in males) HFD decreased PEA levels ($F_{1,28}=4.96$; $p<0.05$). Regarding OEA, MD increased this endocannabinoid only in males (0.28 ± 0.02 pmol/mg vs 0.47 ± 0.07 pmol/mg; $p<0.05$) and this effect was counteracted by HFD (MD-CD vs 0.30 ± 0.06 pmol/mg; $p<0.01$), whereas in females HFD significantly decreased OEA levels as compared to animals fed with control diet (0.40 ± 0.03 pmol/mg vs 0.24 ± 0.01 pmol/mg; $p<0.05$).

Peri-renal adipose tissue: HFD increased AEA levels in all groups ($F_{1,56}=19.00$; $p<0.001$) and decreased 2-AG content in males ($F_{1,28}=7.43$; $p<0.05$). In turn, MD decreased AEA ($F_{1,28}=14.51$; $p<0.01$) and increased 2-AG ($F_{1,28}=5.20$; $p<0.05$) in females with both effects being attenuated by HFD. No significant effects were found for PEA or OEA.

Subcutaneous adipose tissue: Also in this case HFD increased AEA in all groups ($F_{1,56}=24.43$; $p<0.001$) and decreased 2-AG in males ($F_{1,28}=4.53$; $p<0.05$). A general effect of sex was found for PEA levels ($F_{1,56}=26.93$; $p<0.001$) with females showing lower values than males, whereas for OEA a marked sexual dimorphism was found in control animals with females showing increased content than males (0.27 ± 0.05 pmol/mg vs 1.26 ± 0.09 pmol/mg; $p<0.001$). No significant effect of the treatments was observed for PEA in males, while MD induced a modest but significant increase of this compound in females ($F_{1,28}=11.18$; $p<0.01$). With respect to OEA, males and females were also differentially affected. In males, HFD modestly increased OEA levels (Co-CD vs 0.49 ± 0.03 pmol/mg; $p<0.05$ Co-HFD and vs 0.50 ± 0.09 pmol/mg; $p<0.05$ MD-HFD), whereas in females both, MD (Co-CD vs 0.54 ± 0.11 pmol/mg; $p<0.01$) and HFD (Co-CD vs 0.54 ± 0.11 pmol/mg; $p<0.01$), separately, decreased the levels of this compound, though the combination of both treatments appeared to attenuate this effect.

The present results show for the first time that MD and HFD induce sex dependent differential effects on the main endocannabinoids, AEA and 2-AG, and of AEA-related mediators, OEA and PEA, in the visceral, brown and subcutaneous adipose tissues of rats. Whether or not these alterations are responsible for the observed gender-related metabolic differences in untreated, MD and/or HFD rats will have to be established through pharmacological manipulation of the activity of endocannabinoid, PEA and OEA molecular targets.

Acknowledgments:Ministerio de Ciencia e Innovación BFU2009-10109, Instituto de Salud Carlos III, Redes temáticas de Investigación, RD06/0001/1013, GRUPO UCM 951579