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DECIPHERING THE CENTRAL IMMUNOMODULATORY EFFECTS OF A VORTIOXETINE PRETREATMENT ON THE LPS-INDUCED INFLAMMATORY CASCADE

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Introduction: Neuroinflammation is a widely confirmed key player in the onset and progression of various diseases, including depression [1]. Neuropharmacological research is thus exploring the potential of different therapies to modulate the inflammatory cascade within the central nervous system to achieve better clinical outcomes. The acute peripheral injection of lipopolysaccharide (LPS), the endotoxin derived from Gram negative bacteria, is widely used to study inflammation-associated behavioural changes in animals. It specifically induces the immune cascade and peculiar behavioural alterations 6 and 24 hours after exposure [2]. Noteworthy, the proinflammatory state induced by LPS systemic injection can influence the functionality of both the ventral and dorsal hippocampal subregions, which play a central role in cognitive processes and emotions/stress, respectively [3].
Vortioxetine (VTX) is a novel multimodal antidepressant with interesting clinical effects [4], but its neuromodulatory abilities have not yet been adequately explored. We recently demonstrated that chronic VTX pretreatment prevented the deficit in recognition memory observed in mice 24 hours after a peripheral injection of LPS. On the other hand, at the transcriptional level, LPS-induced upregulation of proinflammatory cytokines observed in mice hippocampus 6 hours post-LPS was not affected by chronic VTX exposure [4].
Aim: To provide a global picture of the molecular mechanisms underlying the behavioural response, herein we assessed the VTX molecular effects 24 h post LPS, investigating transcriptional levels of selected cytokines (IL6, IL1B, TNFα, IL4) in dorsal and ventral hippocampus.
Methods: Adult C57BL/6J male mice (n=34) were fed with standard diet or VTX-enriched diet (600 mg/kg of food, 28 days) and then intraperitoneally injected with LPS (830 μg/kg) or saline solution. Total mRNA was extracted from dorsal and ventral hippocampus and retrotranscribed. Gene expression of IL6, IL1B, TNFα, IL4 was evaluated by Real Time PCR. Statistical analyses were performed using SPSS software: data were analysed with two-way ANOVAs (LPSxdiet). Planned pairwise comparisons were performed by Tukey's post hoc test. P-values below 0.05 were considered statistically significant.
Results: We observed a main effect of LPS in both dorsal ($p<0.001$) and ventral ($p<0.001$) hippocampus on IL1b transcriptional levels, but not of diet. For IL6 expression, no main effect of LPS or diet was revealed in both the hippocampal portions. Regarding TNFα expression levels, two-way ANOVA highlighted a main effect of both LPS and VTX-enriched with a different and specific modulatory effect in each hippocampal subregion: the drug enhanced the proinflammatory effect of LPS in the ventral hippocampus ($p<0.01$), while the LPS-induced TNFα upregulation was dampened by the treatment in the dorsal hippocampus ($p<0.05$). Concerning IL4, a main effect of LPS and VTX-enriched diet were detected in the dorsal ($p<0.05$), but not in the ventral subregion.
Conclusion: VTX interferes selectively and in an area-dependent manner with the inflammatory cascade that is associated with peculiar behavioural alterations in a mouse model of neuroinflammation. This allows to further clarify the molecular mechanisms underlying depression and VTX treatment fostering the identification of more effective therapies for the treatment of a such disabling disease.

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CAN THE 'SOCIAL' OXTR GENE BE CALLED 'THE STRESS RESILIENCE' GENE?

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Introduction: Most people during life experience traumtic events that fill out the first (A) criterion for PTSD diagnosis. Although the reaction to these events is highly heterogenous it seems to be influenced by genes as well. Some individuals will develop PTSD, while some will not even if they experience the same trauma load. PTSD leads to dysregulation on the HPA axis which lead to prone vulnerability to different somatic and psychiatric disorders. In stress situation oxytocin is important for containing low cortizol levels with the aim to turn the body back into the „ pre- stress state" by resolving the HPA dysregulation. Resilience might be influenced by the so-called „ social gene" named oxytocin receptor gene, especially with the SNP rs53576.
We hypothesized that carrying the G allele presents a protective factor for development of posttraumatic stress disorder and related psychopathology.
Methods: Participants (N=719) have been exposed to war-related trauma during the war in South-Eastern Europe. Most of the volunteers have experienced traumatic events related to war and ethnic cleansing in the time frame from 1991-1999, while some of them had not experienced any trauma or never had symptoms of PTSD. Therefore the experimental sample of a total of 719 volunteers was divided into three major groups.The experimental group comprised 218 participants with current PTSD ,151 participants with lifetime PTSD and 350 participants with no diagnosable PTSD. We correlated the presence and absence of current and lifetime PTSD as well as PTSD severity evaluated with the Clinician Administered PTSD scale (CAPS) and current psychopathology by using the Brief Symptom Inventory (BSI) score with the mentioned SNP. DNA was isolated from whole blood and genotyped for OXTR rs53576 following previously published protocols. The SNP was polymorphous (minor allele frequency$\geq$10%), reached a minimal genotyping call rate of 98% and did not deviate from Hardy-Weinberg equilibrium ($p\geq0.1$). Logistic regression was used for case-control analyses by testing all patients of either subgroup. Within the two groups of patients, linear regression was carried out individually for analyses on CAPS and BSI scores. The additive allelic and the genotypic models were tested in all phenotypes. The significance level was Bonferroni adjusted.
Results: Nominally significant results were found for OXTR rs53576 in connection with the CAPS and BSI scores within lifetime PTSD patients. The additive allelic model indicated that G allele carriers achieved lower CAPS ($p=0.0090$) and BSI ($p=0.0408$) scores than participants carrying one or two copies of the A allele. However, these nominal significant results for OXTR rs53576 and CAPS and BSI scores could not be replicated in patients with current PTSD symptoms and did not withstand correction for multiple tests.
Conclusion:Our results provide a new insight into PTSD genetics providing data that the OXTR gene (rs5376 SNP) might play an important role in diagnosis development. In this way we are able to screen for „ genetically" risky patients which then could affect treatment options.However, all socioemotional behaviors are influenced by multiple genes, future research in larger cohorts should address how these genes may interact with others.
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