UMEÅ UNIVERSITET

Umeå University Medical Dissertations, New Series No 2310

PREMENSTRUAL DYSPHORIC DISORDER

Brain structure and function, $GABA_A$-active neurosteroids and $GABA_A$ receptor plasticity

Louise Stiernman

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Bergasalen, byggnad 27, Norrlands Universitetssjukhus, fredagen den 23 augusti, kl. 13:00.

Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Professor Elias Eriksson, Institutionen för Farmakologi, Sahlgrenska akademien, Göteborgs Universitet, Sverige.

Department of Clinical Sciences, Obstetrics and Gynecology

Organization
Umeå University
Department of Clinical Sciences

Document type
Doctoral thesis

Date of publication
24 May 2024

Author
Louise Stiernman

Title
Premenstrual Dysphoric Disorder: Brain structure and function, $GABA_A$-active neurosteroids and $GABA_A$ receptor plasticity

Abstract
Background Premenstrual dysphoric disorder (PMDD) is an ovarian hormone-bound disorder, characterized by mood symptoms which occur exclusively during the luteal phase of the menstrual cycle. Previous neuroimaging studies of PMDD have primarily reported functional brain differences during the luteal phase in regions of the salience network (SN), which is commonly implicated in mood and anxiety disorders. SN dysfunction may mediate affective and behavioral deficits by leading to enhanced detection and inappropriate assignment of salience to stimuli. What drives altered brain function in PMDD is unknown. However, one influential hypothesis implicates the luteal phase hormone progesterone, and in particular its neurosteroid metabolites. Progesterone-derived neurosteroids increase transmission at the γ-aminobutyric acid type A ($GABA_A$) receptor, leading to increased inhibitory tone at the neuronal level. This thesis aimed to i) investigate structural and functional characteristics of the brain in PMDD, ii) relate functional measures to levels of neurosteroids during the luteal phase, and iii) investigate how gene expression of $GABA_A$ receptor subunits is altered across the menstrual cycle in PMDD.

Results In Study I, we found that women with PMDD had thinner cortices in widespread brain regions, including regions of the SN. In Studies II and III, we found that increases in functional brain measures are most prominent during the symptomatic luteal phase in regions belonging to the SN and in other networks commonly involved in the psychopathology of mood disorders. Furthermore, we could show that increased activity in key nodes of the SN was apparent in the follicular phase and related to the severity of affective symptoms experienced during the luteal phase. Additionally, in Study II, we found that functional activity in the amygdala, a key region of the SN, was differentially associated with serum levels of $GABA_A$ receptor-active neurosteroids between PMDD and controls during the luteal phase. Lastly, in Study IV, we found seminal evidence of reduced mRNA expression of the δ-$GABA_A$ subunit, which imbues $GABA_A$ receptors with increased sensitivity to progesterone's neurosteroid metabolites. Lower expression of δ subunits was related to higher amygdala reactivity.

Conclusion In this thesis, I provide evidence for altered structure and function in multiple brain networks, particularly the SN in PMDD. Accentuated SN dysfunction during the symptomatic luteal phase may be mediated by the amygdala, and related to abnormal deficits in the expression of neurosteroid-sensitive δ-$GABA_A$ receptors in response to ovarian hormone fluctuations. It is unclear what drives persistent abnormalities in SN function, but innate factors and neuroplastic changes are proposed to play a role.

Keywords
Premenstrual dysphoric disorder, $GABA_A$ receptor, neurosteroids, allopregnanolone, isoallopregnanolone, functional magnetic brain imaging, salience network

Language
English

ISBN
print: 978-91-8070-419-9
PDF: 978-91-8070-420-5

ISSN
0346-6612

Number of pages
128 + 4 papers