Neural Correlates of Postpartum Depression: Elevated Monoamine Oxidase A (MAO-A) Binding in Prefrontal and Anterior Cingulate Cortex

Julia Sacher[1,2,3], Alan A. Wilson[2], Sylvain Houle[2], Leslie Romano[1,2], Jinoos Hamidi[1], Pablo Rusjan[2], P. Vivien Rekkas[1,2], Donna Stewart[4], & Jeffrey H. Meyer[1,2]

[1]Vivian M. Rakoff PET Imaging Centre at Centre for Addiction and Mental Health, University of Toronto, Canada,
[2]Mood and Anxiety Disorders Division, Centre for Addiction and Mental Health and Department of Psychiatry, and University Health Network, Department of Psychiatry, University of Toronto, Canada,
[3]Clinic of Cognitive Neurology, University of Leipzig and Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany,
[4]Women's Health Program and the Toronto General Research Institute, University Health Network, University of Toronto, Canada.

sacher@cbs.mpg.de

Abstract

Purpose of the study: Determining the neurochemical underpinnings of postpartum depression (PPD) in humans is challenging because post-mortem studies are almost impossible as an investigative tool and the demands of motherhood in combination with PPD make recruitment for neuroimaging studies difficult. The purpose of this Positron Emission Tomography (PET) study was to determine binding of the Monoamine-Oxidase A (MAO-A), an enzyme metabolizing monoamines, in brain regions associated with sad mood and pessimism in women suffering from PPD.

Methods: We have scanned fifteen first onset, antidepressant naive, postpartum depressed subjects who were within 1.5 years since delivery and twenty-one healthy, age-matched women using [^{11}C]-Harmine Positron Emission Tomography (PET) to measure MAO-A total distribution volume (MAO-A V_T) in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), thalamus, putamen, ventral striatum, hippocampus, and midbrain.

Results: In postpartum depression, MAO-A V_T was significantly greater in the PFC and ACC (MANOVA, $F_{2,33} = 7.45$, $p = 0.002$; mean difference 22 % and 20 % respectively). Similar results were found in the other brain regions.

Conclusions: We identified substantial MAO-A binding elevation as a key mechanism for the neurobiology of major depressive episodes (MDE) with postpartum onset. Elevated MAO-A V_T in the PFC and ACC argues that enhanced monoamine lowering and oxidative stressare are important pathophysiological components of PPD and that MAO-A inhibitors should be investigated for treating PPD.

Background

With a prevalence rate of 13 % PPD represents the most common complication of childbearing and increases the lifetime risk for major depressive disorder (MDD) [1, 2]. Monoamine Oxidase A (MAO-A) is elevated during early onset major depressive episodes(MDE) [3] and recurrence of MDE [4]. An index of MAO-A levels is measurable with [^{11}C]-Harmine PET [3, 5]. We have previously identified a neurobiological model for postpartum blues [6] comprised of acute estrogen loss, a significant elevation of MAO-A peaking on day 5 postpartum, and subsequent monoamine-loss. We propose that healthy euthymic women will show a down-regulation of MAO-levels in the brain within the first year postpartum whereas women who develop PPD will continue to show increased MAO-A binding in frontal brain areas. In this study we aim to investigate MAO-A binding in prefrontal cortex and anterior cingulate cortex of PPD and postpartum euthymic women within the first year following delivery. Our primary ROIs were those for which serotonergic depletion has been best demonstrated to influence MAO-A substrate availability [7] (e.g. prefrontal cortex, anterior cingulate cortex).

Methods

15 women who were suffering from PPD and 21 healthy women completed the protocol. (table 1). The absence of any past or present DSM-IV Axis I disorders was determined using the Structured Clinical Interview for DSM-IV nonpatient edition and the Hamilton Scale for Depression. ***PET Imaging*** Each woman underwent a single session of [^{11}C]-Harmine PET scanning. Women refrained from breastfeeding for more than 13 half-lives of the radiotracer (260 minutes) after injection. Radioactivity in breast milk was measured at approximately 250 minutes after injection and was indistinguishable from background activity at that time. [^{11}C]-Harmine was administered as a bolus intravenously, arterial sampling was taken continuously for the first 10 min (ABSS system) and manual samples were taken at 5, 10, 15, 20, 30, 45, 60 and 90 min. Continuous arterial blood radioactivity levels were counted using an ABSS system. Parent and metabolite concentrations were measured using HPLC. [^{11}C]-Harmine was of high radiochemical purity (> 96 %) and high specific acitivity. ***Scanning*** 15 frames of 1 min, then 15 frames of 5 min on Siemens-HRRT (intrinsic resolution-full width at half maximum = 2.8 mm). Transmission scans were acquired using a single point source, 137Cs (T = 30.2 years, Eγ = 662 keV) and used for attenuation correction. ***Analysis*** Regions of interest (ROI) for the prefrontal cortex and the anterior cingulate cortex were drawn on magnetic resonance imaging (GE Signa 1.5 T scanner, T_1 & PD-sequences) scans that were co-registered to each summated [^{11}C]-Harmine PET image using a mutual information algorithm [8]. V_T (total distribution volume) values were obtained using the invasive Logan model.

Tabelle 1

Demographic and Clinical Characteristics of Healthy and Postpartum Depressed Subjects

	Healthy Subjects (n = 21)	Postpartum Depressed Subjects (n = 15)
Age y, mean (SD)	31.43 (7.20)	30.00 (6.20)
Current SCID diagnosis of major depressive episode	0	15
HRSD score on scan day, mean (SD)	.55 (.83)*	20.8 (3.17)
Parity**		
Subjects with 1 child	9	7
Subjects with 2 or more children	7	8
Subjects with 0 children	4	0
Menstrual Cycle		
Follicular phase	9	6
Mid cycle	3	2
Luteal	6	4
Menstrual cycle not returned yet since delivery	3	3

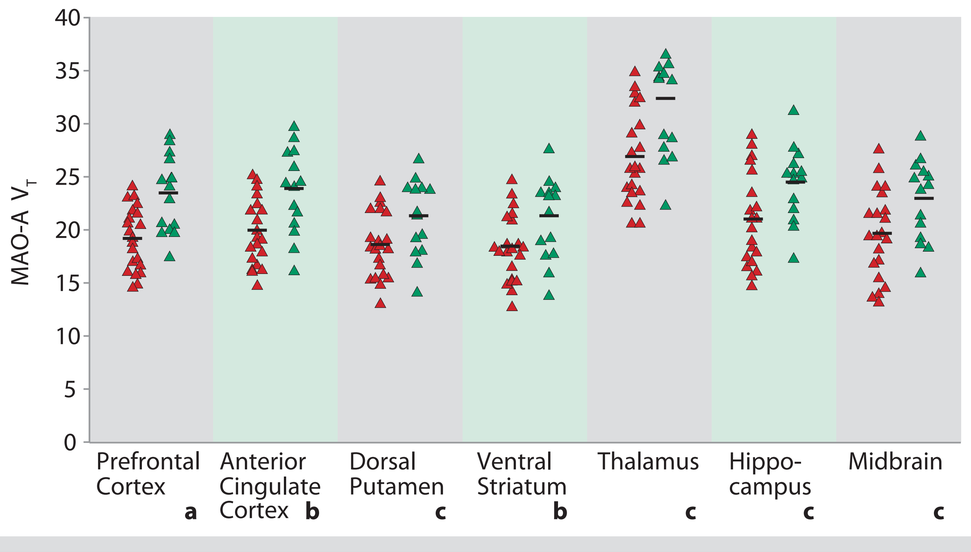
Abbreviations: HRSD, 17-item Hamilton Rating Scale for Depression; SD, standard deviation.
* 20 of the 21 subjects completed the HRSD **At the time of scanning
Independent sample t-test showed no significant difference for age and phase of menstrual cycle.

Results

As shown on the demographics table 1, there were no significant differences in age ($t_{34} = 0.42$, $p = 0.68$) nor phase of menstrual cycle ($t_{34} = 0.44$ to 0.08, $p = 0.66$ to 0.94) at the time of scanning between groups. MAO-A V_T was significantly greater in PPD in prefrontal and anterior cingulate cortex: multivariate analysis of variance (MANOVA), effect of group (PPD versus controls), $F_{2,33} = 7.45$, $p = 0.002$ (see figure 1). MAO-A V_T was also significantly greater in PPD in all brain regions: MANOVA, effect of group (PPD versus controls), $F_{7,28} = 3.10$, $p = 0.015$ (also see figure 1). The mean Edinburgh Depression Scale in the PPD was 15.93 ± 2.84.

1

Greater MAO-A VT Level in Postpartum Depression Compared to Healthy Controls
In postpartum depression, MAO-A VT was significantly greater in prefrontal and anterior cingulate cortex: multivariate analysis of variance, MANOVA, $F_{2,33} = 7.5$, $p = 0.002$. In postpartum depression, MAO-A V_T was also significantly greater in all brain regions: MANOVA, effect of group $F_{7,28} = 3.1$, $p = 0.015$. MAO-A V_T were also compared with an independent *t*-test.
a $p \leq 0.001$, **b** $p \leq 0.005$, **c** $p \leq 0.025$

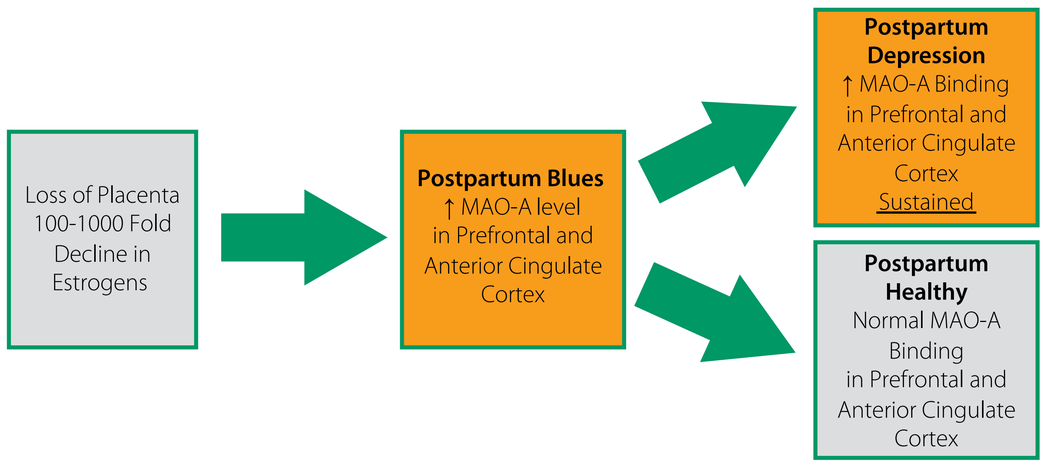


Conclusions

We propose a sustained MAO-A binding elevation as a central neurobiological correlate for postpartum depression (figure 2). We infer that treatment with MAO-A inhibitors should be a considered as a promising strategy in the treatment of severe postpartum depression. Clinical trials investigating the reversible MAO-A inhibitor moclobemide for treatment of postpartum depression would be the next step in this direction. Our findings suggest categorizing PPD as being more similar to early onset major depressive disorder and dissimilar to late onset major depressive disorder (associated with neurodegenerative disease). These findings also have implications for developing novel prevention strategies for PPD that specifically target preventing the persistence of elevated MAO-A levels between early postpartum and subsequent PPD.

2

Model for Development of Postpartum Depression
We propose a chain of events in postpartum starting with a 100 to 1000 fold decreased estrogen, rise in MAO-A binding in regions such as prefrontal and anterior cingulate cortex, and then, based upon the present study, persistence of elevated MAO-A binding in those who get PPD.



References
[1] O'Hara, M.W., and Swain A.M, Rates and risk of postpartum depression – A meta-analysis. *International Review of Psychiatry,* 1996.
[2] Steiner, M., Perinatal mood disorders: position paper. *Psychopharmacol Bull,* 1998.
[3] Meyer, J.H., et al., Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. *Arch Gen Psychiatry,* 2006.
[4] Meyer, J.H., et al., Brain Monoamine Oxidase A Binding in Major Depressive Disorder: Relationship to Selective Serotonin Reuptake Inhibitor Treatment, Recovery and Recurrence. *Arch Gen Psychiatry,* 2009.
[5] Ginovart, N., et al., Positron emission tomography quantification of [11C]-harmine binding to monoamine oxidase-A in the human brain. *J Cereb Blood Flow Metab,* 2006.
[6] Sacher, J., et al., Elevated brain monoamine oxidase A binding in the early postpartum period. *Arch Gen Psychiatry,* 2010.
[7] Lieben, C.K., et al., Acute tryptophan and serotonin depletion using an optimized tryptophan-free protein-carbohydrate mixture in the adult rat. *Neurochem Int,* 2004.
[8] Rusjan, P., et al., An automated method for the extraction of regional data from PET images. *Psychiatry Res*, 2006.

Acknowledgements
This research received project support from the Canadian Institutes of Health Research (CIHR), the National Alliance for Research on Schizophrenia and Depression (NARSAD), Funds for the Advancement of Scientific Research Austria (FWF), the Canadian Foundation for Innovation (CFI), the Ontario Ministry for Research and Innovation, the Ontario Mental Health Foundation (OMHF), the Humboldt Foundation and the Society in Science (SoS). We thank Dr. Alexandra Soliman, research analyst Laura Miler and Cynthia Xu, secretary Natasha Bennett, technicians Alvina Ng and Laura Ng, chemistry staff Jun Parkes, Armando Garcia, Winston Stableford and Min Wong, and engineers Terry Bell and Ted Brandts-Harris for their assistance with this project.

ECNP 2012