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Research report

Tryptophan pathway alterations in the postpartum period and in acute postpartum psychosis and depression

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ABSTRACT

Objectives: Women are at very high risk for the first onset of acute and severe mood disorders the first weeks after delivery. Tryptophan breakdown is increased as a physiological phenomenon of the postpartum period and might lead to vulnerability for affective psychosis (PP) and severe depression (PD). The aim of the current study was to investigate alterations in tryptophan breakdown in the physiological postpartum period compared to patients with severe postpartum mood disorders.
Methods: We included 52 patients (29 with PP, 23 with PD), 52 matched healthy postpartum women and 29 healthy non-postpartum women. Analyzes of serum tryptophan metabolites were performed using LC–MS/MS system for tryptophan, kynurenine, 3-hydroxykynurenine, kynurenic acid and 5-hydroxyindoleacetic acid.
Results: The first two months of the physiological postpartum period were characterized by low tryptophan levels, increased breakdown towards kynurenine and a downstream shift toward the 3-OH-kynurenine arm, away from the kynurenic acid arm. Kynurenine was significantly lower in patients with PP and PD as compared to healthy postpartum women ($p=0.011$ and $p=0.001$); the remaining tryptophan metabolites demonstrated few differences between patients and healthy postpartum women.
Limitation: Low prevalence of the investigated disorders and strict exclusion criteria to obtain homogenous groups, resulted in relatively small sample sizes.
Conclusion: The high kynurenine levels and increased tryptophan breakdown as a phenomenon of the physiological postpartum period was not present in patients with severe postpartum mood disorders. No differences were observed in the levels of the 'neurotoxic' 3-OH-kynurenine and the 'neuroprotective' kynurenic acid arms between patients and healthy postpartum women.

1. Introduction

After childbirth, women are at increased risk of severe mood disorders, such as postpartum psychosis and postpartum depression. Postpartum psychosis (PP) is the most severe childbirth related mood disorder. Although the prevalence is low (1 per 1000 childbirths), women are approximately 22 times more likely to experience the onset of a manic or affective psychotic episode in the first month postpartum than at any other time in their lives (Munk-Olsen et al., 2006). In the majority of cases, the onset is rapid and within 2 weeks postpartum. Early symptoms include insomnia and mood fluctuation, followed by more severe mood symptoms such as mania, depression, or a mixed state, as well as psychotic and cognitive symptoms (Bergink et al., 2011; Sit et al., 2006; Spinelli, 2009). Affective phenomenology is a hallmark of the disease and therefore, postpartum psychosis is generally considered a bipolar spectrum disorder and not a primary psychotic disorder (Boyce and Barriball, 2010). In some women postpartum psychosis is a first manifestation of a life long bipolar disorder, but in other women affective psychosis is entirely restricted to the postpartum period (Bergink et al., 2015a).

Postpartum depression (PD) refers to a non-psychotic depressive episode that affects approximately 10% of mothers after childbirth (Gavin et al., 2005). Women with postpartum depression often experience symptoms of misery, apathy, irritability, social isolation, anxiety, failure to cope and guilt. Postpartum

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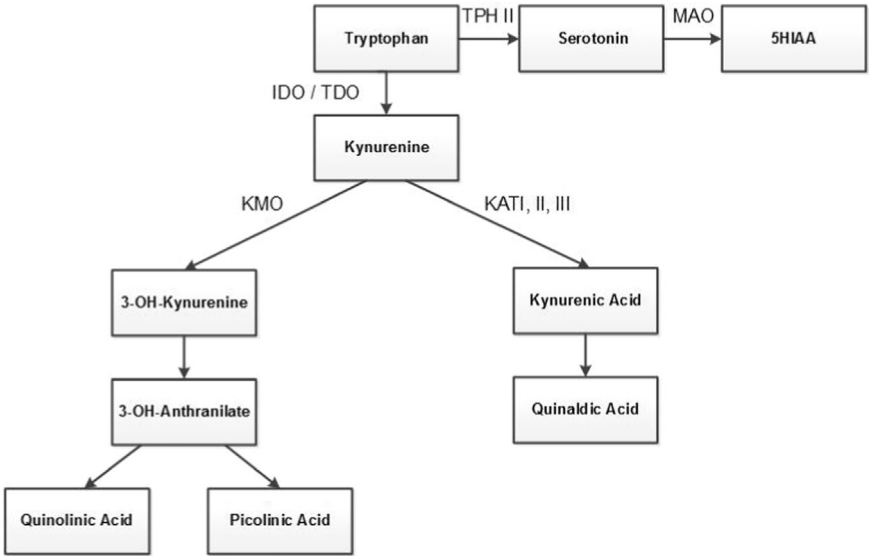

Fig. 1. The tryptophan pathway—the pathways underlying tryptophan metabolism. The main branches are towards the 'neuroprotective' kynurenic acid arm, towards the 'neurotoxic' 3-OH-kynurenine arm and towards the serotonin arm. In the 3-OH-kynurenine arm adenosine-triphosphate (ATP) and nicotinamide-adenine-dinucleotide (NAD) are formed. Legend; IDO = indoleamine-2,3-dioxygenase, TDO = tryptophan 2,3-dioxygenase (TDO), KMO = kynurenine-3-monooxygenase, KAT = kynurenine aminotransferase, TPH = tryptophan hydroxylase, MAO = monoamine oxidase.

depression is highly heterogeneous and both psychosocial status and stressful life events are important risk factors. Half of women with postpartum depression have their onset during pregnancy. Severe depression with an acute onset within the first months postpartum is thought to be a more homogenous subtype within the bipolar spectrum (Sharma and Mazmanian, 2014).

The occurrence of first onset acute and severe episodes (mania, depression, psychotic depression) in the postpartum period is intriguing for both clinicians and researchers, but the underlying mechanism is largely unknown. Mood disorders in general have been associated with monoaminergic neurotransmitter alterations, such as decreased availability of serotonin. A few studies have suggested that the occurrence of postpartum mood symptoms could be related to increased tryptophan breakdown (Fig. 1), a physiological phenomenon of pregnancy and the postpartum period (Kohl et al., 2005; Maes et al., 2002). During pregnancy, tryptophan metabolism is altered, with a decrease in total tryptophan and a shift in the proportions of free and bound tryptophan (Badaway, 2014). After pregnancy, both free and bound tryptophan levels gradually return to pre-pregnancy levels (Handley et al., 1977; Schrocksnadel et al., 1996, 2003). The downstream tryptophan pathway beyond the degradation to kynurenine has never been investigated in women with severe postpartum mood disorders, but there is evidence for major alterations in severe mood disorders outside the postpartum period (Myint et al., 2007a, b; Ogawa et al., 2014; Savitz et al., 2015a, b). Increased breakdown via the tryptophan–kynurenine pathway augments serotonin deficiency, which could serve as a potential etiological factor for mood disorders. In addition, tryptophan breakdown leads to an increased formation of kynurenine and downstream products, some of which are known to have neurotoxic properties (Okuda et al., 1998; Schwarcz et al., 1983).

Tryptophan-2,3- dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) are enzymes in the degradation of tryptophan to kynurenine (Kyn). TDO is mainly induced by glucocorticoids (Bender, 1983) and IDO is particularly induced under the influence of pro-inflammatory cytokines (Capuron et al., 2002) (Fig. 1). Further downstream, Kyn is either metabolized to kynurenic acid (KynA) by the kynurenine aminotransferases (KAT) enzymes, or to 3-OH-kynurenine (3HK) under the influence of the enzyme kynurenine-3-monooxygenase (KMO). Similar to IDO, KMO is activated by pro-inflammatory cytokines (Chiarugi et al., 2001; Zunszain et al., 2012). Several products in the 3HK pathway are toxic for neurons: 3HK contributes to neurodegeneration by inducing neuronal apoptosis (Okuda et al., 1998) and quinolinic acid is a well-known excitotoxin (Schwarcz et al., 1983). KynA protects against the neurodegenerative excitotoxic action of quinolinic acid, balancing the two arms of the system (Kim and Choi, 1987). Activation of the inflammatory response system can lead to an imbalance in the tryptophan degradation pathway including high tryptophan breakdown (due to activation of IDO) and a shift towards the more neurotoxic pathway (due to KMO activation).

The aim of the current study is to investigate if alterations in tryptophan degradation in the postpartum period are associated with the occurrence of postpartum depression and postpartum psychosis. We measured tryptophan pathway metabolites in both healthy postpartum and healthy non-postpartum women to examine the normal physiological changes that occur during the postpartum period. Moreover, we investigated the association of tryptophan metabolism with postpartum psychosis and postpartum depression compared to healthy postpartum women. We hypothesized that the physiological enhancement of the tryptophan breakdown pathway is aggravated in patients with postpartum psychosis and postpartum depression, considering their previously demonstrated inflammatory character (Bergink et al., 2013; Gleicher, 2007; Osborne and Monk, 2013).

2. Methods and materials

2.1. Participants

This study protocol was approved by the institutional review board of the Erasmus Medical Center, Rotterdam (original protocol number MEC-2005226). After receiving a complete description of the study, all patients provided written informed consent.

Fifty-two ($n=52$) patients with a severe postpartum onset psychiatric disorder (PP or PD) were recruited from the Mother–Baby Inpatient Unit of the Department of Psychiatry of the Erasmus Medical Center in Rotterdam, the Netherlands between