

Developmental and psychoneuroimmunological mechanisms in depression

Citation for published version (APA):

Pujol-Lopez, Y. (2015). *Developmental and psychoneuroimmunological mechanisms in depression*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20151030yp>

Document status and date:

Published: 01/01/2015

DOI:

[10.26481/dis.20151030yp](https://doi.org/10.26481/dis.20151030yp)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Valorization

Psychiatric disorders have a large impact on our society. More than 350 million people are estimated to suffer from depression including an increasing number of young persons. Concretely, major depression is the leading cause of disability with a high social, economic and societal burden (WHO 2012). Patients suffering from depression show a reduced capacity to study or work, which considerably affects the economy (Gilbody, Bower et al. 2012, McTernan, Dollard et al. 2013). Moreover, suicide and divorce rates are increased in depressed patients (Wolfersdorf 2008).

Major depression is a heterogeneous and complex disorder compromising a wide spectrum of symptoms, such as low mood, insomnia, fatigue and anhedonia among others (Kennedy 2008). There still is a lack of knowledge of the underlying cause of depression, which dramatically complicates its diagnosis and treatment. Diagnosis is still based on a clinical psychiatric interview, due to the lack of suitable biomarkers. Treatment consists mainly of antidepressants, which increase the concentration of monoamine neurotransmitters in the synaptic cleft. However, it is still unclear whether the therapeutic effect of antidepressants is related to their monoaminergic actions. For instance, while antidepressants rapidly increase monoamine levels, weeks or months of treatment are required before clinical improvement is observed. In addition, treatment efficiency is only 60-65%, with a remission rate of around 30% (Block and Nemeroff 2014), and at least 20% of depressed patients are treatment-resistant (Berlim and Turecki 2007). In view of the high societal burden, it is vital to deepen our understanding of the biological mechanisms of depression in order to unveil new potential therapeutic targets, such as the kynurenine pathway.

Depression has been linked to inflammation, since a subgroup of depressed patients show higher circulating levels of pro-inflammatory cytokines (amongst other increased inflammatory markers), and major depression is frequently comorbid with many inflammatory diseases (Anisman and Hayley 2012, see review by Gray and Bloch 2012). Interestingly, cytokines regulate several enzymes of the kynurenine pathway (Myint 2012), leading to the production of several neurotoxic, e.g. quinolinic acid (QUIN), metabolites. Thus, the kynurenine pathway has been considered as a possible mechanism involved in the pathophysiology of depression (Maes, Mihaylova et al. 2007, Myint, Kim et al. 2007, Miura, Ozaki et al. 2008) and its metabolites and enzymes may serve as potential biomarkers (Fukuda 2014).

Many studies have examined the levels of different metabolites of the kynurenine pathway in depressed patients (Sublette, Galfalvy et al. 2011, Ogawa, Fujii et al. 2014, Savitz, Drevets et al. 2015). However, the full range of metabolites in conjunction with the expression of genes involved in the kynurenine pathway has not been examined yet. In this thesis, we show increased levels of some considered neurotoxic metabolites of the pathway e.g. kynurenine (KYN), 3-hydroxykynurenine (3HK) and QUIN, as well as increased expression of the enzymes regulating this arm of the pathway. In addition, the negative association observed between the kynurenic acid/kynurenine (KYNA/KYN) ratio and scores in the Montgomery-Asberg Depression Rating Scale (MADRS), underscores that development of depressive symptoms is mediated by a disturbance in neuroprotective support. Altogether, we found altered levels of neurotoxic and

neuroprotective metabolites in IFN- α treated patients, consolidating the possible use of these metabolites as biomarkers for depression.

In particular, QUIN has been studied extensively, because of its known neurotoxic effects (Nemeth, Toldi et al. 2005). Although physiological levels of QUIN are necessary in healthy conditions to synthesize nicotinamide adenine dinucleotide (NAD), which is needed for any cell to function properly (Myint 2012), evidence is lacking regarding QUIN in normal physiological conditions. Therefore, in Chapter 4 we investigated in the brain of naïve mice the localization of QUIN, the pattern of its staining, and its possible association with a subset of affect-related behavioural phenotypes. We detected QUIN-immunoreactivity, particularly in the cingulate cortex and the thalamic reticular nucleus (TRN), and it was strongly correlated with locomotor activity in males. This suggests an important role for QUIN at the level of the TRN in regulating motor behaviour. Interestingly, the TRN has been involved in attention-deficit hyperactivity disorder (ADHD), specifically in the modulation of arousal (di Michele, Prichep et al. 2005, Rowe, Robinson et al. 2005). In addition, recently a study reported that the QUIN/3HK ratio was positively correlated with psychomotor agitation in depressed subjects (Halaris, Myint et al. 2015). To sum up, we show that QUIN is observed in normal conditions in the brain and that it may play a role in the regulation of motor behavior. Thus, the conception of QUIN just as a neurotoxic factor should be further clarified.

Another mechanism that has been associated with depression is epigenetic programming. Specifically, changes in histone acetylation have been involved in the pathophysiology of depression (Tsankova, Berton et al.

2006). In addition, histone deacetylase (HDAC) inhibitors have been reported to exert antidepressant effects (Yamawaki, Fuchikami et al. 2012, Hsing, Hung et al. 2015) and have been suggested as possible targets for the future development of novel antidepressant treatments (Covington, Maze et al. 2009). Therefore, we studied changes in epigenetic processes in a maternal immune activation mouse model for depression using a viral mimetic, e.g. polyinosinic:polycytidylic acid (Poly I:C). We observed an increase in global HDAC enzymatic activity, particularly in females' offspring exposed prenatally to Poly I:C. Further investigations on the specific HDAC isoforms involved and the effects produced by HDAC inhibitors, would be of great value.

To conclude, this thesis aimed to provide more evidence on the current approaches to diagnose and treat depression. Our results are certainly of interest to subjects undergoing IFN- α or pro-inflammatory cytokine therapy and to depressed patients suffering from an inflammatory condition. To our knowledge, we are the first to analyse the complete KYN pathway in conjunction with the gene expression levels of the enzymes involved, in IFN- α induced depression. Besides, we combined the measurements of global DNA methyltransferase (DNMT) and HDAC activity with specific HDAC isoform measures. Our studies support further investigation in the use of HDAC inhibitors as new targets for the treatment of depression. In addition, we reaffirmed the use of metabolites of the kynurenine pathway, e.g. KYN, 3HK and QUIN and the enzymes regulating this neurotoxic arm, kynureninase (KYNase) and kynurenine-3-monooxygenase (KMO), as

potential biomarkers for the diagnosis of depression. These metabolites and enzymes mentioned above could also be used to differentiate depressed patients with or without underlying inflammatory conditions. In addition, their measurement before and after treatment, might help in the prediction of the therapeutic response.

References

- Anisman, H. and S. Hayley (2012). Inflammatory Factors Contribute to Depression and Its Comorbid Conditions.
- Berlim, M. T. and G. Turecki (2007). "Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods." Canadian Journal of Psychiatry **52**(1): 46.
- Block, S. G. and C. B. Nemeroff (2014). "Emerging antidepressants to treat major depressive disorder." Asian Journal of Psychiatry **12**(0): 7-16.
- Covington, H. E., 3rd, I. Maze, Q. C. LaPlant, V. F. Vialou, Y. N. Ohnishi, O. Berton, D. M. Fass, W. Renthal, A. J. Rush, 3rd, E. Y. Wu, S. Ghose, V. Krishnan, S. J. Russo, C. Tamminga, S. J. Haggarty and E. J. Nestler (2009). "Antidepressant actions of histone deacetylase inhibitors." J Neurosci **29**(37): 11451-11460.
- di Michele, F., L. Prichep, E. R. John and R. J. Chabot (2005). "The neurophysiology of attention-deficit/hyperactivity disorder." Int J Psychophysiol **58**(1): 81-93.
- Fukuda, K. (2014). "Etiological classification of depression based on the enzymes of tryptophan metabolism." BMC Psychiatry **14**: 372.
- Gilbody, S., P. Bower and J. Rick (2012). "Better care for depression in the workplace: integrating occupational and mental health services." The British Journal of Psychiatry **200**(6): 442-443.
- Gray, S. M. and M. H. Bloch (2012). "Systematic Review of Proinflammatory Cytokines in Obsessive-Compulsive Disorder." Current psychiatry reports **14**(3): 220-228.
- Halaris, A., A. M. Myint, V. Savant, E. Meresh, E. Lim, G. Guillemin, D. Hoppensteadt, J. Fareed and J. Sinacore (2015). "Does escitalopram reduce neurotoxicity in major depression?" J Psychiatr Res **66-67**: 118-126.
- Hsing, C.-H., S.-K. Hung, Y.-C. Chen, T.-S. Wei, D.-P. Sun, J.-J. Wang and C.-H. Yeh (2015). "Histone Deacetylase Inhibitor Trichostatin A Ameliorated Endotoxin-Induced Neuroinflammation and Cognitive Dysfunction." Mediators of Inflammation **501**: 163140.
- Kennedy, S. H. (2008). "Core symptoms of major depressive disorder: relevance to diagnosis and treatment." Dialogues in Clinical Neuroscience **10**(3): 271-277.
- Maes, M., I. Mihaylova, M. D. Ruyter, M. Kubera and E. Bosmans (2007). "The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation." Neuro Endocrinol Lett **28**(6): 826-831.

- McTernan, W. P., M. F. Dollard and A. D. LaMontagne (2013). "Depression in the workplace: An economic cost analysis of depression-related productivity loss attributable to job strain and bullying." *Work & Stress* **27**(4): 321-338.
- Miura, H., N. Ozaki, M. Sawada, K. Isobe, T. Ohta and T. Nagatsu (2008). "A link between stress and depression: shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression." *Stress* **11**(3): 198-209.
- Myint, A. M. (2012). "Kynurenines: from the perspective of major psychiatric disorders." *FEBS Journal* **279**(8): 1375-1385.
- Myint, A. M., Y. K. Kim, R. Verkerk, S. Scharpe, H. Steinbusch and B. Leonard (2007). "Kynurenine pathway in major depression: evidence of impaired neuroprotection." *J Affect Disord* **98**(1-2): 143-151.
- Nemeth, H., J. Toldi and L. Vecsei (2005). "Role of kynurenines in the central and peripheral nervous systems." *Current neurovascular research* **2**(3): 249-260.
- Ogawa, S., T. Fujii, N. Koga, H. Hori, T. Teraishi, K. Hattori, T. Noda, T. Higuchi, N. Motohashi and H. Kunugi (2014). "Plasma L-tryptophan concentration in major depressive disorder: new data and meta-analysis." *J Clin Psychiatry* **75**(9): e906-915.
- Rowe, D. L., P. A. Robinson, I. L. Lazzaro, R. C. Powles, E. Gordon and L. M. Williams (2005). "Biophysical modeling of tonic cortical electrical activity in attention deficit hyperactivity disorder." *Int J Neurosci* **115**(9): 1273-1305.
- Savitz, J., W. C. Drevets, B. E. Wurfel, B. N. Ford, P. S. Bellgowan, T. A. Victor, J. Bodurka, T. K. Teague and R. Dantzer (2015). "Reduction of kynurenic acid to quinolinic acid ratio in both the depressed and remitted phases of major depressive disorder." *Brain Behav Immun* **46**: 55-59.
- Sublette, M. E., H. C. Galfalvy, D. Fuchs, M. Lapidus, M. F. Grunebaum, M. A. Oquendo, J. John Mann and T. T. Postolache (2011). "Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder." *Brain, Behavior, and Immunity* **25**(6): 1272-1278.
- Tsankova, N. M., O. Berton, W. Renthal, A. Kumar, R. L. Neve and E. J. Nestler (2006). "Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action." *Nat Neurosci* **9**(4): 519-525.
- WHO (2012). "Depression: A Global Crisis. World Mental Health Day, October 10 2012. World Federation for Mental Health. Available: http://www.who.int/mental_health/management/depression/wfmh_paper_depression_wmhd_2012.pdf."
- Wolfersdorf, M. (2008). "[Depression and suicide]." *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **51**(4): 443-450.

Yamawaki, Y., M. Fuchikami, S. Morinobu, M. Segawa, T. Matsumoto and S. Yamawaki (2012). "Antidepressant-like effect of sodium butyrate (HDAC inhibitor) and its molecular mechanism of action in the rat hippocampus." World J Biol Psychiatry **13**(6): 458-467.