Hindawi Publishing Corporation

Cardiovascular Psychiatry and Neurology

Cardiovascular Psychiatry and Neurology
Volume 2009 (2009), Article ID 187894, 5 pages
doi:10.1155/2009/187894

Hypothesis

Interleukin-10: A Key Cytokine in Depre

Susana Roque, Margarida Correia-Neves, Ana Raquel Mesquita, Joa
and Nuno Sousa

Life and Health Sciences Research Institute, School of Health Scien
Minho, Campus Gualtar, 4710-057 Braga, Portugal

Received 8 May 2009; Accepted 23 June 2009

Academic Editor: Hari Manev

Abstract

An increasing body of evidence implicates proinflammatory cytoki
Of notice, recent studies showed that anti-inflammatory cytokin
behavior. In this article, we propose that the anti-inflammatory cy
most widely reported phenomenon observed in depressed patie
adrenal axis and the imbalanced production of cytokines. If
antidepressant therapy.

1. Introduction

The establishment of a bidirectional interaction between the immu
remarkable findings of the last decades. These two systems accor
body of evidence shows that both share common mediators, inclu
altered expression of these molecules, triggered by one of the sys
[1]. As a consequence, a disruption in this cross-talk has been
associated with several psychiatric disorders, in particular depressi

Major depression is a global public-health problem and a leading ca

contributor to the global burden of disease in 2000 (in terms of D/
is a heterogeneous disorder with a variable set of symptoms, dive
treatment. The etiology of depression is still controversial, and se
into account the communication between the immune and cent
proposed a role for cytokines in depression [4]. The “cytokine th
in the last two decades, proposes that enhanced production of
pathogenesis of depression. Indeed, several studies show a signifi
cytokines (namely, IL-6, IL-1 , IFN- , and TNF) among depressed
on the administration of IFN- and IL-2, which is frequently used
and certain cancers, has been associated with depressed mood a
[8 – 10]. The fact that the symptoms associated with depression
cytokine administration supports a causal role for cytokines in th
relieved by the administration of antidepressant drugs [11].

The “cytokine theory of depression” has also been supported by
using these models demonstrated that alteration in the proinfla
changes overlapping with those found in depressed patients, i
dysfunction, and altered sleep patterns [12]. In further support
(CMS) protocol, which induces symptoms of depressive-like b
hippocampus [13]. Furthermore, the depressive-like behavior o
administration of IL-1 [13] and, when mice lacking the expressio
paradigm, the behavioral changes do not occur [13]. Interestingly
of the cytokines more consistently upregulated in depression, sh
(FST), that is, decreased signs of depressive-like behavior in
considered one of the gold standard tests to evaluate depression
TNF activation also mediates depressive-like behavior in mice.

Although most studies on the “cytokine theory of depression” a
cytokines, the role of anti-inflammatory cytokines has been rece
important anti-inflammatory cytokines, proved to be relevant i
expression of IL-10 (IL-10KO) show a decreased latency to immob
(WT) mice in the FST [15]. These results demonstrate that IL-10K
sign of depressive-like behavior in rodents. Remarkably, administ
phenotype observed in the IL-10KO animals [15]. In further suppo
overexpressing this cytokine show a decreased depressive-like be
[15]. In addition to the increased helplessness in mice that lack t
that modulation of IL-10 impacts on psychophysiological alteratio
is the impairment in sleep behavior [16]. Interestingly, IL-10KO r
exogenous administration of IL-10 modulates sleep behavior [17 –

Another feature commonly associated with depression is altered
using the IL-10KO mouse model, that the absence of this anti-in
nociception (i.e., the ability to sense painful stimuli). This study sh
time to paw licking (the time that mice spend to avoid a heat stim
with WT mice, and this result was confirmed by the blockage of IL
evidence that IL-10 can also be involved in the common biological

The studies described above show that modulation of IL-10 impact
namely, helplessness, sleep disturbances, and pain perception.
these symptoms which suggests a putative antidepressant eff
relevance for this hypothesis is the observation, in depressed pa
increased IL-10 levels after treatment with several classes of antid

Although it is becoming clear that modulation of IL-10 can lead t
animals, the mechanisms behind these alterations remain to be
through which IL-10 influences behavior. One of the most obviou
cytokine may have on the levels of proinflammatory cytokines. In t
10KO mice, leads to an increased production of proinflammatc
“cytokine theory of depression”, trigger depression. This mec
depressive-like behavior in IL-10KO mice upon IL-10 administratic
of proinflammatory cytokines [26]. However, this possibility is nc
detect two of the most relevant proinflammatory cytokines (IFN-
studies are certainly necessary to clearly define how the lack of Il
cytokines as it is possible that subtle (below currently detectic
cytokines are present in the serum of IL-10KO mice, and/or that
proinflammatory cytokines in specific brain regions, which may not

The observations that systemic IL-10 administration to WT animal
increased motor activity and abnormal exploratory patterns) [27]
like behavior observed in IL-10KO mice [15] indicate that perip
system. However, it is not clear how this cytokine acts within the
IL-10 does not seem to cross the intact blood-brain barrier, at lea
10, like other cytokines, acts directly in the brain through regi
circumventricular organs and the choroid plexus, or by activatin
signals to specific brain nuclei [5]. Moreover, IL-10 has been dete
Possible sites of expression are the endothelial cells of the brain c
(from where it would be secreted into the cerebrospinal fluid), and
a recent study showed that several immune mediators are produ
inflammatory stimuli [32]. In addition, the IL-10 receptor has bee
oligodendrocytes [29, 30, 33]; probably because of a general dis
the receptor in all five brain regions they analyzed (cortex, cereb
[34].

A direct action of IL-10 within the central nervous system might b
10 has been shown to prevent cell death of glial cells [33, 35, 36]
Since an increase in neuronal apoptosis in the hippocampus has
[38], this putative role of IL-10 in increasing neuronal survival sh
action in preventing depressive-like behavior.

The observation that IL-10KO mice show an increase in the adre
[15] offers another alternative mechanism for the action of IL-10
pituitary-adrenal (HPA) axis. Indeed, it was shown that, even in b
corticosterone and that in the presence of a stressor the increase
WT mice [39]. These findings strongly suggest that IL-10 may ha
most consistent neurobiological alterations in depressed subjec
associated with impaired HPA axis glucocorticoid feedback sensi
plausible that IL-10 modulation of depressive-like behavior is
accordance, IL-10 is able to suppress, in a dose dependent man
steroid production in adrenal cells [41]. This effect appears to
responsible for the biosynthetic pathway of corticosterone [21, 4
expressed in the zona fasciculata (the region responsible for the p
gland [41]. Accordingly, in vivo studies demonstrated that, under
HPA axis activation, such as increased adrenal glands, decreas
corticosterone [15, 39]. These findings strongly suggest that IL-
production by the adrenal gland [41]. A microarray analysis of
treated with IL-10 clearly showed that this anti-inflammatory cyto
genes of the HPA axis [42]. Of notice, murine pituitary cells were t

10 [43], and the presence of IL-10 was also found in human pitu pituitary, IL-10 seems to have the same effect already described f positive regulation of corticotrophin releasing factor (CRF) and AC noticed that while the studies in the hypothalamus and pituitary w IL-10 in corticosterone production by the adrenal gland is a more vivo studies. Taking into account that depression is often assoc hypothesize that IL-10 has a pivotal role in the modulation of the impact on the etiology of depression.

Increases in glucocorticoid levels can occur daily in response to s an enhanced production of IL-10 [47] which, in normal situations, the HPA axis (Figure 1(a)). However, if these raises in glucocortic "resistance to glucocorticoid action" [40, 48]. In fact, impaired r a hallmark of major depression and is reflected by decreased r resistance to glucocorticoids was also described in IL-10 producing decrease in the production of IL-10 which might impact on the neg adrenal glands. In addition, decreased IL-10 can promote an im activate the HPA axis (Figure 1(b)). This hypothesis fits well wit glucocorticoids trigger a proinflammatory action [49].

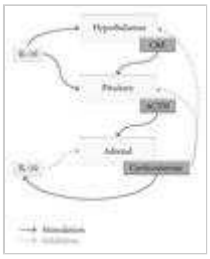

Figure 1: Schematic representation of the li situation and (b) during depression.

In the hypothesis outlined here we proposed IL-10 as an impo cytokine milieus that are of recognized relevance for depressio represent a link between the modulation of neural, endocrine, a further understand the etiology of depression. The cross-talk b become a target for novel antidepressant therapies.

Acknowledgments

The authors acknowledge the Portuguese Foundation for Science Roque S. (SFRH/BD/24539/2005). This work was supported by a G

References

1. D. Wrona, "Neural-immune interactions: an integrative vie and immune systems," *Journal of Neuroimmunology*, vol. 1
2. M. R. Irwin and A. H. Miller, "Depressive disorders and imm *Behavior, and Immunity*, vol. 21, no. 4, pp. 374–383, 2007
3. S. Moussavi, S. Chatterji, E. Verdes, A. Tandon, V. Patel, an decrements in health: results from the World Health Survey 2007.
4. R. S. Smith, "The macrophage theory of depression," *Med*

5. C. L. Raison, L. Capuron, and A. H. Miller, "Cytokines sing t depression," *Trends in Immunology*, vol. 27, no. 1, pp. 24 -
6. M. Maes, "Evidence for an immune response in major depre *Neuropsychopharmacol and Biological Psychiatry*, vol. 19, pp
7. H. Anisman, A. V. Ravindran, J. Griffiths, and Z. Merali, "Er depression and dysthymia with typical or atypical features," 1999.
8. L. Capuron and A. H. Miller, "Cytokines and psychopatholog *Psychiatry*, vol. 56, no. 11, pp. 819–824, 2004.
9. S. Bonaccorso, H. Meltzer, and M. Maes, "Psychological and *Opinion in Psychiatry*, vol. 13, no. 6, pp. 673–677, 2000.
10. M. Maes, S. Bonaccorso, V. Marino, et al., "Treatment with induces lower serum dipeptidyl peptidase IV activity, which i symptoms and immune activation," *Molecular Psychiatry*, v
11. D. L. Musselman, D. H. Lawson, J. F. Gumnick, et al., "Paro high-dose interferon alfa," *New England Journal of Medicine*
12. R. Dantzer, J. C. O'Connor, G. G. Freund, R. W. Johnson, an and depression: when the immune system subjugates the br pp. 46–56, 2008.
13. I. Goshen, T. Kreisel, O. Ben-Menachem-Zidon, et al., "Bra depression in mice via adrenocortical activation and hippoca *Psychiatry*, vol. 13, no. 7, pp. 717–728, 2008.
14. B. B. Simen, C. H. Duman, A. A. Simen, and R. S. Duman, behavioral consequences of individual receptor targeting," 2006.
15. A. R. Mesquita, M. Correia-Neves, S. Roque, et al., "IL-10 r *Psychiatric Research*, vol. 43, no. 2, pp. 89–97, 2008.
16. R. H. Belmaker and G. Agam, "Major depressive disorder," pp. 55–68, 2008.
17. M. R. Opp, E. M. Smith, and T. K. Hughes Jr., "Interleukin- central nervous system of rats to reduce sleep," *Journal of* 1995.
18. T. Kushikata, J. Fang, and J. M. Krueger, "Interleukin-10 in *Interferon and Cytokine Research*, vol. 19, no. 9, pp. 1025–
19. L. A. Toth and M. R. Opp, "Cytokine- and microbially induce mice," *American Journal of Physiology*, vol. 280, no. 6, pp.
20. M. J. Bair, R. L. Robinson, W. Katon, and K. Kroenke, "Depr *Archives of Internal Medicine*, vol. 163, no. 20, pp. 2433–24
21. H. Tu, T. Juelich, E. M. Smith, S.K. Tyring, P. L. Rady, and T interleukin-10 during nociception," *Journal of Neuroimmun*
22. M. Kubera, M. Maes, V. Holan, A. Basta-Kaim, A. Roman, an increases the production of interleukin-10, an anti-inflamma

chronic mild stress model of depression," *Journal of Affecti*
2001.

23. M. Kubera, A.-H. Lin, G. Kenis, E. Bosmans, D. van Bockstae
antidepressants through suppression of the interferon-γ/inte
Psychopharmacology, vol. 21, no. 2, pp. 199–206, 2001.

24. G. Kenis and M. Maes, "Effects of antidepressants on the pr
Neuropsychopharmacology, vol. 5, no. 4, pp. 401–412, 200

25. M. Maes, C. Song, A.-H. Lin, et al., "Negative immunoregul
interferon-γ and stimulation of interleukin-10 secretion," *N*
379, 1999.

26. K. W. Moore, R. de Waal Malefyt, R. L. Coffman, and A. O'Ga
receptor," *Annual Review of Immunology*, vol. 19, pp. 683

27. D. Harvey, R. Smith, K. English, B. Mahon, and S. Commins
Lipopolysaccharide (LPS) produces increased motor activity
spatial learning in Balb/c mice," *Physiology and Behavior*, v

28. A. J. Kastin, V. Akerstrom, and W. Pan, "Interleukin-10 as
brain/blood-spinal cord barrier," *Molecular Brain Research*,

29. L. Vitkovic, S. Maeda, and E. Sternberg, "Anti-inflammatory
NeuroImmunoModulation, vol. 9, no. 6, pp. 295–312, 2001

30. A. Ledeboer, J. J. P. Brevé, A. Wierinckx, et al., "Expressio
10 receptor in rat astroglial and microglial cells," *European*
1185, 2002.

31. N. Quan and W. A. Banks, "Brain-immune communication
21, no. 6, pp. 727–735, 2007.

32. F. Marques, J. C. Sousa, G. Coppola, et al., "Kinetic profile
choroid plexus by peripheral inflammation," *Journal of Cere*
921–932, 2009.

33. E. Molina-Holgado, J. M. Vela, A. Arévalo-Martín, and C. Gua
cells: role of nitric oxide and protection by the anti-inflamma
Neuroscience, vol. 13, no. 3, pp. 493–502, 2001.

34. H. Ward, S. Vigues, S. Poole, and A. F. Bristow, "The rat in
cDNA coding for the alpha-chain protein sequence, and dem
rat brain," *Cytokine*, vol. 15, no. 5, pp. 237–240, 2001.

35. K. Pahan, M. Khan, and I. Singh, "Interleukin-10 and interl
ceramide production through the activation of phosphatidyli
75, no. 2, pp. 576–582, 2000.

36. K. Strle, J.-H. Zhou, S. R. Broussard, et al., "IL-10 promote
Journal of Neuroimmunology, vol. 122, no. 1-2, pp. 9–19, 2

37. A. Bachis, A. M. Colangelo, S. Vicini, et al., "Interleukin-10
cell death by blocking caspase-3-like activity," *Journal of N*

38. P. J. Lucassen, G. K. Vollmann-Honsdorf, M. Gleisberg, B. Cz
psychosocial stress differentially affects apoptosis in hippoca
shrew," *European Journal of Neuroscience*, vol. 14, no. 1, p

39. E. M. Smith, P. Cadet, G. B. Stefano, M. R. Opp, and T. K. H and brain," *Journal of Neuroimmunology*, vol. 100, no. 1-2,

40. C. L. Raison and A. H. Miller, "When not enough is too muc the pathophysiology of stress-related disorders," *American* 1565, 2003.

41. N. Koldzic-Zivanovic, H. Tu, T. L. Juelich, et al., "Regulatior 10: a preponderance of IL-10 receptor in the adrenal zona fa 20, no. 5, pp. 460–468, 2006.

42. H. Tu, P. L. Rady, T. Juelich, et al., "Interleukin-10 regulate pituitary-adrenal axis origin," *Cellular and Molecular Neurol*

43. T. K. Hughes, P. Cadet, P. L. Rady, S. K. Tyring, R. Chin, an action of interleukin-10 in pituitary cells," *Cellular and Mole* 1994.

44. P. L. Rady, E. M. Smith, P. Cadet, M. R. Opp, S. K. Tyring, a transcripts in human pituitary and hypothalamus," *Cellular* 289–296, 1995.

45. A. V. Turnbull and C. L. Rivier, "Regulation of the hypothala and mechanisms of action," *Physiological Reviews*, vol. 79,

46. G. B. Stefano, V. Prevot, J.-C. Beauvillain, and T. K. Hughes releasing factor median eminence in rats: evidence for depe *Neuroscience Letters*, vol. 256, no. 3, pp. 167–170, 1998.

47. A. O'Garra and F. J. Barrat, "In vitro generation of IL-10-pr immunosuppressive drugs and inhibited by Th1- and Th2-inc no. 2, pp. 135–139, 2003.

48. C. Hawrylowicz, D. Richards, T.-K. Loke, C. Corrigan, and T. production in T lymphocytes from corticosteroid-resistant as *Immunology*, vol. 109, no. 2, pp. 369–370, 2002.

49. S. F. Sorrells and R. M. Sapolsky, "An inflammatory review *Behavior, and Immunity*, vol. 21, no. 3, pp. 259–272, 2007