A roadmap for investigating the role of the prion protein in depression associated with neurodegenerative disease

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ABSTRACT. The physiological properties of the native, endogenous prion protein (PrP\textsuperscript{C}) is a matter of concern, due to its pleiotropic functions and links to neurodegenerative disorders and cancer. In line with our hypothesis that the basic function of PrP\textsuperscript{C} is to serve as a cell surface scaffold for the assembly of signaling modules, multiple interactions have been identified of PrP\textsuperscript{C} with signaling molecules, including neurotransmitter receptors. We recently reported evidence that PrP\textsuperscript{C} may modulate monoaminergic neurotransmission, as well as depressive-like behavior in mice. Here, we discuss how those results, together with a number of other studies, including our previous demonstration that inflammatory and behavioral stress modulate PrP\textsuperscript{C} content in neutrophils, suggest a distributed role of PrP\textsuperscript{C} in clinical depression and inflammation associated with neurodegenerative diseases. An overarching understanding of the multiple interventions of PrP\textsuperscript{C} upon physiological events may both shed light on the pathogenesis of, as well as help the identification of novel therapeutic targets for clinical depression, Prion and Alzheimer’s Diseases.

KEYWORDS. Alzheimer’s disease, depression, prion, inflammation, monoaminergic neurotransmission, microglia, neutrophil, neurodegeneration

INTRODUCTION

Whereas the main focus in the field of prion biology has been the conformational conversion of the prion protein (PrP\textsuperscript{C}) into abnormal, disease-related forms, there is growing interest in physiological roles of PrP\textsuperscript{C}.\textsuperscript{1-3} A wide range of functions have now been claimed for PrP\textsuperscript{C} at the molecular, cellular and system levels,\textsuperscript{2} but such an embarrassment of riches has done little for the understanding of the basic biological function of the prion protein. We have, therefore, proposed that PrP\textsuperscript{C} serves as a cell surface scaffold for the assembly of signaling modules.\textsuperscript{2,4} Accordingly, dynamic interactions with cell type- and context-dependent ligands may...
explain its pleiotropic regulation of signaling pathways, which translates into wide-range consequences upon both physiology and behavior.2

The prion protein abounds in synapses,5,6 where contributions to neurotransmission may strongly affect both neural function and dysfunction. Modulation by PrP\(^\text{C}\) of several neurotransmitter systems has been reported, albeit in each case the strength of the evidence for direct interaction is somewhat variable7-14. A phage display screen conducted in our laboratory identified group I metabotropic glutamate receptors (mGluR1/5) as a putative binding partner of PrP\(^\text{C}\), which was originally validated in the context of signal transduction triggered by the interaction of PrP\(^\text{C}\) with laminin,15 and subsequently by PrP\(^\text{C}\)-dependent effects of oligomers of the A\(\beta\) peptide,16 the latter of which fuel the ongoing debate over the role of PrP\(^\text{C}\) in the pathogenesis of Alzheimer Disease.17

Novel hits of our phage display indicated both the serotonergic receptor 5HT\(_{5A}\) and the SERT serotonin transporter as putative binding partners of the prion protein (T. A. Americo, M. H. Magdesian and R. Linden, unpublished), and recent results are consistent with the hypothesis of an interaction of PrP\(^\text{C}\) with monoaminergic systems.18 Thus, binding of PrP\(^\text{C}\) to 5HT\(_{5A}\), SERT, as well as to the dopamine receptor D1R, but not to D4R, was detected in overlay assays, and co-localized immunolabeling of both 5HT\(_{5A}\) and D1 with PrP\(^\text{C}\) was found in confocal photomicrographs of the cerebral cortex of wildtype mice. In addition, differing responses were found between wildtype and PrP\(^\text{C}\)-null cerebrocortical tissue probed with either serotonin or dopamine, but not noradrenaline, which were at least partly conveyed by 5HT\(_{5A}\) and D1 with PrP\(^\text{C}\) was found in confocal photomicrographs of the cerebral cortex of wildtype mice. In addition, differing responses were found between wildtype and PrP\(^\text{C}\)-null cerebrocortical tissue probed with either serotonin or dopamine, but not noradrenaline, which were at least partly conveyed by 5HT\(_{5A}\) and D1, respectively. These effects were accompanied in Prnp-null tissue by differential contents of both the 5HT\(_{5A}\) (but not 5HT\(_{1A}\)) receptor and of dopamine, the latter likely associated with an increased content of tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of dopamine. Concurring behavioral tests characterized depressive-like behavior in the Prnp-null mice,18 in line with an earlier report from other investigators, where such behavioral changes were counteracted by either imipramine, a tricyclic antidepressant, or the NMDA receptor antagonist MK-801.19

The interpretation of our findings as evidence for an interaction of PrP\(^\text{C}\) with monoaminergic systems has been challenged on the basis of the flanking gene problem, that is the persistence in congenic knockout mice of allelotypes of bystander genes closed linked to the targeted gene.20 Thus, a given polymorphism of one such gene, present in the embryonic stem cells used for the production of the original transgenic animals, is expected to remain linked for many generations, to the adjacent targeted locus in mixed strains used for propagation of the knockout genotype. In the present case, the issue was specifically referred to a previous demonstration21 that hyperphagocytosis of apoptotic bodies by macrophages derived from Prnp-null mice, originally reported by our group,22 was traced to the Prnp-flanking gene Sirpa, that encodes Signal Regulatory Protein \(\alpha\) (SIRP\(\alpha\)). This protein affects immune responses inclusive of phagocytosis by macrophages,23 and a specific polymorphism of the Sirpa gene (henceforth designated 129Sirpa) is present in both the 129Sv and 129Ola mouse strains that originated the knockout of Prnp, but not in the mouse strains employed for propagation of such genotype, namely C57/BL6 or C57/B110SnJ, which led, respectively, to current colonies of mixed B6.129Sv and B10.129Ola mice.21

However, the inference20 that the 129Sirpa polymorphism is responsible for the depressive-like phenotype identified in our Prnp-null mice is unwarranted.24 First, a study invoked as precedent for the role of Sirpa in depressive-like behavior,25 indeed showed that mice expressing a form of SIRP\(\alpha\) that lacks most of its cytoplasmic region manifest impaired responses in the forced swim test (FST), but there was no effect upon the Tail Suspension test (TST).25 In contrast, our Prnp-null mice differed from wildtype not only in FST, but also in TST, as well as in the additional Novelty Supressed Feeding test, all of which are taken as indicators of depressive-like behavior in rodents. Also differing from our results,18 the engineered SIRP\(\alpha\) produced no change in
dopamine levels. Moreover, the same truncated SIRPa reportedly leads to robust neuroprotection against ischemic damage, similar to deletion of its major ligand CD47, whereas ischemic damage is aggravated in Prnp-null mice, thus corroborating the evidence that effects of either Prnp deletion or truncated Sirpa do not overlap. In addition, other studies in our lab, using the same B10.129Ola strain, failed to show immune phenotypes expected to appear in either neutrophils or microglia of Prnp-null mice as a consequence of the 129Sirpa polymorphism. The possibility that our colony may have lost the differential effect of the Sirpa polymorphism derived from the 129Ola background is currently under investigation.

Together with the evidence that PrPC may indeed bind to both serotonergic and dopaminergic receptors, the functional changes detected in our studies are consistent with the hypothesis that the prion protein plays a role in the activity of monoaminergic systems and upon depressive-like behavior. Here we discuss a framework for investigating the extended hypothesis that PrPC may be involved in major depression associated with neurodegenerative conditions, with focus on the Transmissible Spongiform Encephalopathies (TSEs, or Prion Diseases) and Alzheimer’s Disease (AlzD).

THE PRION PROTEIN AND MONOAMINERGIC SYSTEMS

Evidence that PrPC modulates serotonergic function was first described in 1C11 murine neuroectodermal cells, when these were induced to express at least the 5-HT1B/D and 5-HT2A serotonergic receptors, and synthesize, store and transport serotonin. Antibody binding to PrPC at the surface of 1C11 serotonergic cells led to recruitment to lipid rafts of PrPC, caveolin and soluble tyrosine kinases, as well as serotonergic receptors, and prevented signal transduction through the latter. Interestingly, 1C11 cells infected with scrapie (PrPC) produced oxidized derivates from serotonin or catecholamines, leading to monoaminergic dysfunction. Interaction with the dopaminergic system was first tested by overexpressing PrPC in a PC12 pheochromocytoma cell line, which resulted in increased content of monoamine oxidase, followed by a reduction in the release of dopamine and increased levels of the dopamine metabolite 3,4-dihydroxyphenylacetic acid. Recently, it was reported that Prnp-null mice showed increased spontaneous climbing, a motor dysfunction related to dopaminergic transmission, whereas in the striatum, PrPC was found in dopaminergic neurons and levels of D1 receptor were reduced, but with no change in dopamine content. Direct interaction was also reported between the C-terminal domain of PrPC and the N-terminal domain of TH, together with evidence that PrPC helped the internalization of the enzyme. Conversely, TH modulated the content of PrPC and its localization in the plasma membrane. However, differing from both this and a previous study, we found no motor deficits in our Prnp-null mice. Notably, the lack of motor symptoms in 8-12 week-old mice, as used in our study, concurs with previous evidence that motor deficits in Prnp-null are restricted to aging animals.

MONOAMINERGIC DYSFUNCTION IN PRION AND ALZHEIMER’S DISEASES

Monoaminergic dysfunction is often found in animals infected with PrPC, as well as in TSEs. Levels of serotonin, dopamine, norepinephrine and their metabolites, as well as the activity of receptors and related enzymes were reportedly changed in scrapie infected animals. Among other modifications, hyperactivity of tryptophan hydroxylase and monoamine oxidase A, increased levels of the metabolite 5-HIAA, and increased turnover of serotonin were reported in TSEs. Further, decreased levels of TH were described in early stages of the conversion of PrPC, associated with a substantial decrease in dopamine and norepinephrine levels in the brain of mice infected with various scrapie strains.

In turn, in the context of AlzD, Prnp-null mice carrying familial AD transgenes encoding
APPswe and PSen1ΔE9, failed to present the extensive serotonin axonal degeneration in the cerebral cortex typical of their Prnp<sup>+/−</sup> counterparts, thus suggesting that Aβ0-PrPC binding is involved in the serotonergic dysfunction presented in AD.46

**CLINICAL DEPRESSION ASSOCIATED WITH PRION AND ALZHEIMER’S DISEASES**

Despite the current consensus that major depression involves far more than the classical monoamine hypothesis,47 evidence of interaction of PrPC with monoaminergic systems warrants the question of whether and how the prion protein may be involved in clinical depression associated with neurodegenerative diseases. Mood disorders are frequent in prion diseases,48 and depletion of both monoaminergic cells and markers was found in the brains of such patients.49-52 Interestingly, tricyclic antidepressants such as imipramine, and antipsychotic drugs such as chlorpromazine, which showed some effect upon psychiatric symptoms in TSE patients,48,53 also inhibited prion replication in vitro.54,55

Monoaminergic systems are also involved in behavioral and psychological symptoms of dementia,56,57 and the prevalence of depression has been reported at up to 50% in AlzD.58,59 Both morphological and functional changes were described in the monoaminergic system of AD patients’ brains,60,61 often associated with worsening clinical symptoms, but it is still uncertain whether these changes are compensatory, adaptive mechanisms, or direct consequences of AD progression. Notably, however, dopaminergic transmission has been hypothesized as a new player in AD pathophysiology,62 and AD patients treated with dopaminergic agonists showed some positive results in restoring LTP-like cortical plasticity.63 Studies in animal models of AD showed that monoaminergic drugs prevented intraneuronal amyloid deposition,64 and either selective serotonin reuptake inhibitors (SSRI) or a high tryptophan diet reduced Aβ production and accumulation.65,66

**INFLAMMATION AND DEPRESSION IN NEURODEGENERATIVE DISEASES**

Both systemic inflammation and neuroinflammation are associated with the progression of neurodegenerative diseases, and may play a major role in their pathogenesis.67-70 A number of co-morbidities/risk factors may contribute to neurodegeneration specifically through modulation of inflammatory responses.70,71 Within the brain, microglial activation, reactive astrocytosis, and the release of a variety of cytokines have been reported in both experimental models and in patients of both TSEs and AlzD.68,72-75

Microglia and/or microglial dysfunction have been identified as a major factor in a chronic inflammatory state associated with both experimental and human clinical prion diseases,67,76,77 as well as in AlzD.70 Recent studies along this line have challenged the previously proposed roles of NLRP3, ASC, and TREM2 in the pathogenesis of experimental prion infections,78,79 but evidence persists of an involvement in microglial proliferation,80 the fractalkine pathway,81 and reactive oxygen species produced by NOX2.82

Microglia has also been directly implicated in major depressive disorder.83,84 Classical antidepressants reportedly inhibit the production of proinflammatory factor such as TNF-α and nitric oxide, and suppress the activation of microglia.85,86 Injection of Aβ oligomers into the mouse brain caused both memory impairment and depressive-like behavior, along with the release of pro-inflammatory cytokines and microglial activation, which were prevented by treatment with a selective serotonin reuptake inhibitor.87 Thus, microglia dysfunction may play a major role in linking depression with AlzD through neuroinflammation.88 Still, despite the evidence for both similarities as well as differences between the neuroinflammatory components of either TSEs or AlzD,68,89 neither a possible role of microglia in linking depression with prion diseases, nor the role of PrPC in Aβ oligomer-induced depressive-like behavior have been specifically examined to date.
Notably, the role of PrP<sup>C</sup> upon microglial biology is still unclear. Differential properties were reported as a function of PrP<sup>C</sup> content in a microglial cell line, as well as in primary microglial cultures from the brains of either wildtype and Prnp-null B6.129Sv mice. In contrast, no difference was found between primary cultures of brain microglial cells from either Prnp-null or wildtype mice of our B10.129Ola colony with regard to cell morphology, expression of the microglial marker Iba1, translocation of NF-κB to the nucleus, cytokine production, levels of iNOS or, notably, either rates of phagocytosis or migration, even following activation.

Besides microglia, however, PrP<sup>C</sup> is widely expressed in the immune system, including human T and B lymphocytes, monocytes, dendritic cells, platelets, and neutrophils. In particular, despite long-standing recognition that neutrophils are involved in the interplay of immune responses with clinical depression, these cells have been largely neglected in the context of the contribution of systemic inflammation to neurodegenerative diseases. Early work indicated that the scrapie agent affects neutrophil biology, whereas conflicting data have been reported regarding an association of neutrophil dysfunction with Alzheimer's disease.

Nevertheless, recent studies warrant an examination of the hypothesis that neutrophils may play a role in the association of depression with neurodegenerative diseases.

A recent study of two transgenic mouse models, as well as of the brains of human AD patients, provided evidence that neutrophils adhere to blood vessels and invade the brain parenchima, release neutrophil extracellular traps (NETs) and interleukin-17, and gather around areas with Aβ aggregation.
amyloid deposits. This chain of events depends on the LFA-1 integrin, blockade of which, as well as depletion of neutrophils, reduced AlzD-like pathological hallmarks and ameliorated cognitive dysfunction in the transgenic mice. Remarkably, neutrophil depletion or inhibition dramatically reduced microglial activation, showing for the first time a microglia-neutrophil crosstalk in AD pathogenesis. This elegant study suggests that neutrophils are major players in the pathogenesis of AlzD, and strongly interact with microglia in the inflammatory responses associated with neurodegeneration. In turn, neutrophils were also implicated in the depressive-like behavior of mice subject to peripheral inflammatory stress, which is known to worsen the course of neurodegeneration in mouse models of both TSEs and AlzD. Thus, polymorphonuclear cells may be instrumental for the relationship among inflammation, depression and neurodegeneration.

Evidence that PrP<sup>C</sup> may be involved in this context stems from our demonstration that inflammatory stress induced overexpression of Prnp, and an increase in the content of PrP<sup>C</sup> at the surface of mouse neutrophils. This effect is mediated by a combination of TGF-β and glucocorticoid, and results in enhanced cytotoxicity of neutrophils toward vascular endothelial cells. It is tempting to speculate that, upon peripheral inflammatory conditions, PrP<sup>C</sup>-overexpressing neutrophils may help disrupt the blood-brain barrier, and invade the central nervous system, thus leading to an impact in both depressive-like behavior, as well as aggravation of neurodegeneration. Our data showing that non-inflammatory restraint stress produced similar effects as inflammatory stress may also be relevant for the suggested, though still controversial link of chronic emotional stress with the course of neurodegenerative conditions.

**CONCLUSION**

Beyond the purported effects of misfolded conformers of the prion protein upon transmissible spongiform encephalopathies, interest in unraveling the functional properties of the normal conformer of PrP<sup>C</sup> has now extended from TSEs to AlzD. Our hypothesis that the biological function of PrP<sup>C</sup> is to provide a cell surface scaffold for the assembly of signaling modules implies that selective interactions with components of signaling systems explain its pleiotropic functions in intercellular interactions both among nerve cells and between the nervous system and other cell types.

Current studies have focused on the triad inflammation-depression-neurodegeneration, as a major determinant of the course of both TSEs and AlzD. This paradigm suggests that the examination of interactions of PrP<sup>C</sup> with monoaminergic pathways, on the one hand, and PrP<sup>C</sup> content and function in effectors of inflammatory reactions, such as microglia and neutrophils, are crucial for an informed approach to the understanding of the pathogenesis of neurodegenerative conditions. Various studies reviewed above are indeed consistent with intervention of PrP<sup>C</sup> in both monoaminergic function and inflammatory events.

Much of the evidence for such roles of PrP<sup>C</sup> is still indirect, and at times circumstantial. Nevertheless, the available data converge upon a framework illustrated in Figure 1, a concerted approach to which may allow the identification of novel therapeutic targets for Prion and/or Alzheimer’s diseases.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

No potential conflicts of interest were disclosed.

**FUNDING**

The authors’ research is supported by grants and fellowships from the Brazilian Council of Scientific and Technological Development (CNPq) and the Foundation for Research Support of the State of Rio de Janeiro (FAPERJ).

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