In Focus

Does asymmetric dimethylarginine play a role in depression in chronic kidney disease patients?

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Depression is a pervasive disorder involving mood, thought and body function. It causes discomfort and moral pain to the depressed person and his/her family and close social contacts. This disorder manifests by a series of symptoms that alter sleep, eating habits, work capacity and the ability to enjoy pleasant life activities. Depression may be a sporadic phenomenon but it usually recurs during lifetime. Without appropriate treatment, a depressive episode may last for years and may not resolve. Importantly, depression is a proteiform condition and may occur within the context of other chronic illnesses such as heart disease or chronic kidney disease (CKD) where it stands as the most frequent mental problem [1]. A recent meta-analysis carried out on 55,982 CKD patients showed that about one-quarter of such patients are depressed. The prevalence of depression increases in parallel with the severity of CKD [2] and may depend on the type of substitutive treatment in patients with end-stage renal disease [3]. It is associated with poor outcomes in dialysis patients, and depressive symptoms predict a higher risk of mortality and cardiovascular events [4] as well as an increased risk of hospitalization [5]. This association is also true in pre-dialysis CKD patients where the presence of depression predicts progression to kidney failure, hospitalization or death independently of age, race, serum haemoglobin, albumin, phosphorus, comorbidities and kidney disease severity [6]. Overall these studies suggest that depression should not be considered as a mere surrogate of other CKD comorbidities and that it may be an independent risk factor for adverse clinical outcomes in these patients. Behavioural factors such as non-adherence to medical treatment, poor nutrition, unhealthy life style and lack of social interactions [7, 8] as well as biological factors including genetic background [9], inflammation and impaired immune status [10] may concur to explain the association between depression and adverse outcomes in this population.

BIOCHEMICAL MECHANISM(S) UNDERLYING DEPRESSION: NITRIC OXIDE, BRAIN-DERIVED NEUROTROPHIC FACTOR AND NEURAL PLASTICITY

Mechanisms underlying the risks of depression are intensively investigated. The observation that altered serotonin levels are associated with enhanced platelet aggregation and vasoconstriction reveals a neural mechanism whereby depression can lead to coronary events in depressed patients in the general population [11]. Several lines of evidence point to nitric oxide (NO) dysregulation as a biological pathway involved in the high cardiovascular (CV) risk associated to depression. NO is involved in several major cellular functions including neurotransmission, regulation of blood vessel tone and immune response. In the central nervous system, NO participates in the regulation of synaptic plasticity [12]. NO interacts with many intracellular targets and is able to trigger an array of signal transduction pathways resulting in stimulatory or inhibitory output signals. Physiological amounts of NO are neuroprotective whereas an over-production of this gas is noxious [13]. Indeed, NO can undergo oxidative-reductive reactions to form cyotoxic compounds which in turn give rise to 'nitrosative stress', an alteration involved in major neurodegenerative disorders [14]. On the other hand, not only high but also low NO bioavailability is harmful for brain cells. In this respect, asymmetric dimethylarginine (ADMA), a major endogenous inhibitor of NO synthase, has been implicated in depressive disorders [15]. Depressive symptoms have indeed been associated with high ADMA levels and low L-arginine/ADMA ratio in...
patients with chronic hepatitis C infection [16] or heart failure [17] and in the elderly [18]. High ADMA is a hallmark of CKD [19]. Thus, this methylarginine is a plausible risk factor for CKD-associated depression. Emerging evidence suggests that interference of ADMA with mental functioning may depend on the effect of this methylarginine on a fundamental neurotransphin, the brain-derived neurotrophic factor (BDNF).

Experimental and clinical studies in depressed adults demonstrate altered neural plasticity including neuronal loss and a reduction in the total volume of the hippocampus [20]. BDNF is a critical mediator of neuronal plasticity in the developing and adult nervous system [21]. BDNF is a Janus molecule, its function being mediated by two specific receptors [i.e. tropomyosin-related kinase receptor B (TrKB) and pan75 neurotrophin receptor (p75NTR)] which promote opposite effects on neuronal plasticity. BDNF–TrKB signalling stimulates neurogenesis, neurite arborization and synaptogenesis while BDNF–p75 signalling causes neurite retraction, neuronal apoptosis and synaptic pruning. The balance between the ‘anabolic’ and ‘catabolic’ effect of BDNF is central to optimizing the development and maintenance of neural networks. Decreased BDNF expression entails neurodegeneration and aberrant neuronal network function, and this neurotrophin is currently considered a likely player in depressive disorders [22]. A meta-analysis published in 2008 retrieved 20 studies including 1504 subjects investigating the link between BDNF and depression. In the aggregate analysis, BDNF levels increased significantly after antidepressant treatment, and BDNF levels and depression scores were significantly and inversely interrelated. The results of this meta-analysis were robust and were confirmed in sensitivity analyses with no evidence for publication bias [23].

**DEPRESSION IN DIALYSIS PATIENTS: AN ADMA AND BDNF AFFAIR?**

In the current issue of *Nephrology Dialysis and Transplantation*, Jan Kielstein et al. [24] report an interesting pilot study exploring the role of ADMA and BDNF in depression in stage 5D (haemodialysis) CKD patients (Figure 1). The study includes a series of experiments in animal models and a small survey in a group of haemodialysis patients. The specific hypothesis tested in these studies is that high ADMA levels may induce depression by altering BDNF levels. Anxiety and locomotor activity in the rat were tested with the hole-board apparatus, an approach frequently applied in behavioural pharmacology studies. This apparatus consists of an enclosed board with regular, crossing lines delimiting quadratic areas each containing a hole at the centre. In this test, changes in head-dipping activity (into the holes of the board) are considered to reflect anxiety [25]. Subtotally (5/6) nephrectomized rats showed signs of major anxiety (time spent until first hole investigation) and decreased motor activity (number of lines crossed in a given time on the board). In this rat model of advanced renal insufficiency, the L-arginine/ADMA ratio was significantly lower than in the intact control rats, whereas plasma ADMA levels were only slightly higher than in the same control animals. Interestingly, immunohistochemistry studies in subtotally nephrectomized rats showed a reduced expression of hippocampal BDNF but similar plasma BDNF as compared with control rats. However, in ADMA-infused rats, serum BDNF levels were significantly lower than those observed in both 5/6 nephrectomized and control, intact rats. Overall observations by Kielstein et al. broadly implicate ADMA in depressive behavioural changes in the rat and suggest that BDNF may be the effector molecule conducive to depressive behaviour in this animal model of chronic renal insufficiency. Apparently, observations in rats co-incident with findings in haemodialysis patients. Indeed, in a small series of 11 patients, serum BDNF was strongly associated in an inverse fashion with the severity of depression, as measured by Beck Depression Inventory (BDI). In general, experiments in rats and cross-sectional analyses in haemodialysis patients in this pilot study generate the fascinating hypothesis that ADMA, a compound which accumulates in end-stage renal disease and which has been associated with a variety of alterations, ranging from cardiovascular complications to several endocrine disturbances and bone disease [26], is a major player in depression in these patients.

**LIGHTS AND SHADES OF THE ADMA HYPOTHESIS OF DEPRESSION IN CKD**

This hypothesis-generating study has numerous weak points. First, the series of haemodialysis patients where the BDNF–BDI score relationship was tested is very small (n = 11), and the abstraction of this series from the source dialysis population is scarcely defined. Of note, the average age of this population was far lower than the average age of haemodialysis patients in Germany, and no information on comorbidities, an important potential confounder, was given. Thus, the very strong inverse relationship between BDNF levels and BDI (r = −0.81, shared variance = 65%) should to be confirmed in larger and better characterized series of haemodialysis patients. Furthermore, no evidence emerged in these cross-sectional analyses that BDNF could be the effector mechanism whereby ADMA may induce depression in these patients. A large amount of circulating BDNF is stored in platelets [27], and serum BDNF levels are ~200-fold higher than plasma levels [28]. Therefore, variations

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**FIGURE 1**: Putative pathways whereby ADMA may be implicated in depression in CKD patients.
in serum BDNF levels may reflect changes in platelet release rather than changes in brain BDNF metabolism [29], suggesting a distinct biological significance for serum and plasma BDNF. In the present study, both in patients and in rats, BDNF was measured in serum. Therefore, circulating BDNF in the present study hardly reflects brain BDNF. As to the experimental part of the present paper, the degree of internal coherence of findings in studies in the hole-board apparatus in rats was modest. For example, direct exploratory behaviour was reduced in 5/6 nephrectomized rats as compared with control rats but it was slightly above normal in intact, ADMA-infused rats, and an identical pattern emerged also for the ‘hole investigation time’ (a metric of anxiety). Thus, to date, ADMA per se fails to account for altered responses to hole-board testing in a model of advanced chronic renal insufficiency in the rat, and the putative ADMA–BDNF link in haemodialysis patients still remains unclear.

In conclusion, as it often occurs in exploratory investigations, in this pilot study by Kielstein et al. [24] there is light and shade, and perhaps the shade, rather than the light, still dominates the scene. Nonetheless, these stimulating observations may pave the way for a new series of experiments in animal models and observations in CKD and haemodialysis patients to investigate in depth the fascinating hypothesis that inhibition of the NO system by endogenous ADMA or other ADMA-dependent effects may be implicated in depressive disorders in CKD patients. Given the public health relevance of depression and CKD, future studies on this issue may produce fruitful knowledge for advancing the understanding of the complex link between these two major chronic disorders.

(See related article by Kielstein et al. Role of the endogenous nitric oxide inhibitor asymmetric dimethylarginine (ADMA) and brain-derived neurotrophic factor (BDNF) in depression and behavioural changes: clinical and preclinical data in chronic kidney disease. *Nephrol Dial Transplant* 2015; 30: 1699–1705.)

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