

Sickness behavior versus clinical depression: from inflammation to oxidative/nitrosative stress, autoimmune responses to neoepitopes, and neuroprogressive pathways

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The first inkling that depression is an immuno-inflammatory disorder and that there are phenomenological similarities between clinical depression and sickness behavior and that both conditions may share a common pathway, i.e. inflammation, was published between 1990-1993 [1-3]. There are some phenomenological similarities between sickness behavior and clinical depression, e.g. behavioral inhibition, anorexia, weight loss, sleep and psychomotor disorders; physio-somatic symptoms (fatigue, hyperalgesia, malaise); anxiety; and mild cognitive impairment [3,4]. Nevertheless, clinical depression and sickness behavior are two completely different conditions [4]. Sickness behavior is an acute behavioral complex induced by acute infections and immune trauma and caused by pro-inflammatory cytokines. It is an adaptive response that enhances recovery by conserving energy to combat infection/inflammation and therefore is a behavioral part of a compensatory (anti)-inflammatory response system (CIRS), which limits an overzealous immuno-inflammatory response [4]. Clinical depression, on the other hand, is a lifelong disease with a tendency towards recurrent episodes, a chronic course, seasonal variation, (hypo)manic symptoms, sensitization of episodes, and progressive deterioration [4-7]. In clinical depression, and not sickness behavior, immuno-inflammatory response 2 sensitization, progressive damage by oxidative and nitrosative stress (O&NS) to fatty acids, proteins, DNA and mitochondria, and progressive autoimmune responses directed against self-epitopes (e.g. anchorage molecules and serotonin) are the substrate of a neuroprogressive process, whereby multiple depressive episodes cause neural tissue damage and consequent functional and cognitive sequelae [4-11]. Whereas sickness behavior is an acute CIRS response, clinical depression is accompanied by a CIRS response that tends to downregulate the primary immuno-inflammatory response [4]. Whereas acute infections/trauma typically elicit sickness behavior, less well defined trigger factors are associated with the onset of depression, i.e. psychosocial stressors and inflammatory disease. While traumatic life events quite likely cause an inflammatory state often leading to clinical depression, no association between psychosocial stressors and sickness behavior has been described. Clinical depression shows multiple “co-morbidities” with a large variety of a) brain disorders related to neurodegeneration, e.g. Alzheimer’s, Parkinson’s and Huntington’s disease, multiple sclerosis and stroke; b) medical disorders, such as cardiovascular disorder, chronic fatigue syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel disease, irritable bowel disease, leaky gut, diabetes type 1 and 2, obesity and the metabolic syndrome, and HIV infection; and c) conditions, such as hemodialysis, interferon- α -based immunotherapy and the postnatal period [12]. The common denominator of all these conditions is activation of (neuro)inflammatory and O&NS pathways. The presence of concomitant depression is strongly associated with a lower quality of life and increased morbidity and mortality in these medical diseases/conditions. All in all, while sickness behavior is an acute, beneficial CIRS response, clinical depression is a disabling, progressive disorder belonging to the spectrum of inflammatory-neurodegenerative diseases. 3

It follows that rather than targeting only one immuno-inflammatory pathway, such as inflammation (e.g. cyclooxygenase-2 or the tryptophan catabolite (TRYCAT) pathway), a better strategy for depression treatment entails the multi-targeting of the relevant pathways, including a) inflammatory cytokines, such as IL-1, IL-6 and TNF α ; b) Th1 and Th17 responses; c) damage by O&NS and lowered antioxidant levels; d) autoimmune responses to oxidatively/nitrosatively modified neoantigenic determinants; e) damage to mitochondria and respiratory chain enzymes and adenosine triphosphate production; and f) neuroprogression [11]. A number of new drug candidates, which we will test in phase-2 placebo controlled trials, are discussed.

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