Early Blood Brain Barrier Dysfunctions In The Social Isolation Rat Model Of Psychosis: Relation To NOX-Derived Oxidative Stress

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Oxidative stress has been shown to play a key role in the pathogenesis of psychosis. We previously reported an increased expression of the NADPH oxidase NOX2, as well as of other markers of enhaced free radical production, in specific brain regions of a non pharmacologic animal model of stress-induced psychopathology (Schiavone et al., 2009; 2012), the rat social isolation rearing, which provides a very useful tool to study alterations reminiscent of what observed in psychotic patients (Weiss et al., 2001; Leng et al., 2004). However, initial neuropathological events leading to NOX2 elevations in the brain have not been clarified yet. Here, we investigated early mRNA modification leading to increased cerebral NOX2 expression. Rats were exposed to a short-term social isolation procedure (1 week) and qPCR for genes implicated in the formation and integrity maintenance of the blood-brain barrier (BBB), immunohistochemistry and Western blotting were performed. An increased expression of these genes and related proteins was observed in 1 week-isolated rats with respect to animals reared in group. This was associated to a significant alterations of the expression of specific markers of BBB integrity, as well as of its permeability and enhancement of IL-6 dependent neuroinflammation. Conversely, no changes in NOX2 expression were observed in 1 week-isolated animals with respect to controls. Our study suggests that early loss of BBB integrity precedes NOX2 increase in the brain, most likely being its leading cause. These results provide an innovative approach for the clarification of the pathological link among psychosocial stress, early oxidative stress in the brain, disruption of the BBB and the development of mental disorders, representing a possible molecular pathways for brain vulnerability as crucial contributor for the development of stress-induced psychopathologies.

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