

SUBSTANCE P AND MAJOR DEPRESSION: NK₁ RECEPTOR EXPRESSION, NF-κB ACTIVATION AND CYTOKINE RELEASE IN MONOCYTES FROM PSYCHIATRIC PATIENTS

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Several experimental data suggest a role for substance P (SP) in the pathogenesis of major depression, patients showing immune dysfunction, high blood SP levels and increased release of pro-inflammatory cytokines. We decided to evaluate NK₁ receptor expression, as well as SP and NK₁ agonists' ability to induce cytokine release and NF-κB activation in monocytes from psychiatric patients and healthy volunteers, and to compare SP effects with those induced by phorbol myristate acetate (PMA).

Patients were selected according to the DSM-IV criteria for major depression (MD) and Bipolar Disease type I or II; Hamilton Rating Scale for Anxiety and Depression were used to define the disease and to recruit patients (n=13). Monocytes were isolated from peripheral blood by standard techniques and purified by adhesion; cytokine release was measured by ELISA kits. NK₁ and NK₂ receptor expression in monocytes from healthy subjects and psychiatric patients was evaluated by immunoblotting and quantified as the ratio between the receptor protein and the housekeeping gene, Na⁺/K⁺ ATPase. NF-κB activation was evaluated by both electrophoretic mobility shift assay and p50 subunit ELISA kits.

NK₁ receptor was significantly ($p < 0.001$) less expressed in MD patients (ratio 0.699 ± 0.18 ; n=8) than in healthy subjects, either smokers (5.8 ± 1 ; n=6) or non-smokers (2.066 ± 0.3 ; n=6). NK₁ receptor levels were higher in bipolar (2.74 ± 1.24 ; n=5) than in MD patients. On the contrary, NK₂ receptor levels were significantly ($p < 0.001$) higher in MD patients than in healthy volunteers. Moreover, NK₂ expression in monocytes from bipolar patients was higher than in MD monocytes (2.36 ± 0.7 ; $p < 0.05$). SP and the NK₁ selective agonist [Sar⁹Met(O₂)₁₁]SP induced TNF-α and IL-6 release, which was reverted by the selective antagonist GR71251. Although less potent than PMA, SP and the NK₁ agonist induced NF-κB p50 subunit translocation in monocytes.

These results indicate that SP and neurokinin receptors could be involved in major depression and bipolar disease, even if further studies are needed to better appreciate the SP role in psychiatric disorders.