SUBCHRONIC ADMINISTRATION OF STATINS REDUCES PLASMA AND BRAIN CONTENT OF NEUROACTIVE STEROIDS

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The statins, reversible inhibitors of hydroxy-methyl-glutaryl coenzime-A reductase enzyme, are the first choice treatment for the management of hypercholesterolemia, a condition characterized by high serum cholesterol levels. Cholesterol is the main constituent of biological membranes and the precursor of progesterone (PROG). Two PROG derivatives, allopregnanolone (AP) and tetraidrossideossicorticosterone (THDOC), are among the most positive potent endogenous modulators of $GABA_A$ receptor complex; their administration in pharmacological doses to rodents elicits anxiolytic, sedative-hypnotic and anticonvulsant effects. Previous studies showed that fluctuations of these metabolites may play an important role in several physiological, as pregnancy and parturition, and pathological conditions, as major depression, panic disorder and anxiety. Several studies have suggested that long-term treatment with drugs reducing cholesterol levels may be accompanied by increased impulsivity, aggressivity and appeared of depressive symptoms.
Previous studies in our laboratory have showed that an animal model of depression, the socially isolated rat, in which the plasmatic and cerebrocortical levels of AP and THDOC are reduced, shows an increased aggressivity, major reaction to handling, anxiety-like and conflict-like behaviour. Therefore, we have evaluated the effect of two lipophilic statins, simvastatin and atorvastatin (25mg/Kg, per os, once a day for 30 days), on the levels of PROG and its metabolites. As aspected, the long-term treatment with statins reduced plasmatic total-cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels. Moreover, the treatment with statins reduced cerebrocortical levels of PROG (simvastatin: -50%; atorvastatin: -48%) while AP was reduced after treatment with simvastatin (-60%). At variance, both statins failed to change the abundance of THDOC. In plasma, PROG, AP and corticosterone (CTS) levels were significantly reduced by chronic treatment with simvastatin and atorvastatin (PROG, -75% and -70%; AP, -63% and -45%; CTS, -86% and -85%, respectively), while simvastatin but not atorvastatin reduced the concentration of THDOC (-28%). The reduction in brain and plasma levels of AP and THDOC was not associated with high levels of fear-like behaviour in the elevated plus-maze test. Given that fluctuation of the levels of neuroactive steroids modifies $GABA_A$ receptor plasticity, we are currently investigating the effect of chronic treatment with statins in the abundance of selected $GABA_A$ receptor subunits.