POST-NATAL REPEATED MILD STRESS INDUCES CHANGES IN BRAIN NAD(P)H RECYCLING IN ADULT MALE MICE: ROLE OF THE OPIOID SYSTEM

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Overweight is the leading determinant in the development of type-2 diabetes mellitus, and both conditions in adult humans may have their roots in early events in the life. We evaluated whether in an experimental model in the mouse, i.e., the association of psychological and nociceptive manipulations in neonatal life, which produces long lasting or permanent overweight, and induce also alterations in hormonal and metabolic parameters in non genetically vulnerable mice, induces also an alteration in brain metabolism. Therefore, the present study was designed to explore cellular metabolic and mitochondrial functions in the *ex vivo* mouse somatosensitive cortex (barrel field, IV layer) and hippocampus (CA1) during neuronal activation that was elicited by electrical stimulation, with the aim to verify whether metabolic alterations which can be observed in our stressed mice model could be evidenced in the brain as well, and, if so, whether brain alterations could be put in relationship to mitochondrial function. Stressed mice during lactation period underwent daily brief (10 min) mother deprivation plus sham s.c. injection. At 35 days of age, stressed mice showed consistent elevation of pain threshold versus controls, and as adults (95-180days) consistent increase of body weight increment curve, accompanied by an increase in the food caloric efficiency (0.022 ±0.001 versus 0.034 ± 0.003) whereas naloxone treatment (1.0 mg/kg/day) prevented these alterations. Moreover, as adults, stressed male mice showed consistent increase of plasma corticosterone and adrenocorticotropin, and increase of glycaemia and insulinaemia. Therefore, an association between metabolic and behavioral changes was found. Moreover, we studied mechanisms contributing to stimulus-evoked changes in NAD(P)H fluorescence as a marker of neuronal activation in brain slices of the mouse. Electrical stimuli were set at a frequency (50 Hz), which produced optimal responses and did not induce consistent bleaching of cells. With these stimuli, biphasic fluorescence changes were produced, which were composed of an initial transient decrease ("initial component", 1-3%), followed by a longer lasting transient increase ("overshoot", 1-8%). These responses, which were found to reflect mitochondrial function, were also used to test possible differences between brain function in adult control mice, and in adult mice which underwent repeated stress during lactation period. Preliminary results show that neonatally stressed adult mice have an initial component with similar amplitude, followed by a consistently higher overshoot, while naloxone-treated stressed mice showed an overshoot curve intermediate between controls and stressed. Behavioral changes between groups were also found (LTP, one trial learning, forced swimming test, elevated plus maze). These results may be considered as a new and interesting direction among long-term or permanent changes induced by neonatal stress on brain structures.