GENDER DIFFERENCE IN SEIZURE SENSITIVITY: ROLE OF STEROIDS AND NEUROACTIVE STEROIDS

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Background

To be men or women is one of the most important determinants of human health, and sex-related vulnerability in brain and body development are described in humans for many conditions, including cerebral excitability, metabolic and immune diseases, etc. Experimental studies in male rodents suggest that stressful events during lactation could have a role in determining metabolic-neurophysiological features of the adult life (programming), but sex-dependent dimorphic studies on programming modulation following neonatal stressful procedures and drug treatment are scanty.

Procedures

In male mice, daily neonatal handling, i.e., psychological distress (10 min of maternal separation) associated to a mild painful stimulus (sham injection) for the whole lactation period, produces long term overweight associated with variations in lipid and glucose homeostasis, immunological upset, break-down of some hypothalamus-pituitary-adrenal (HPA) feed-back mechanisms. Upset of hormones levels appear of particular importance for the triggering of said metabolic conditions. In this paper paper we investigate: i) whether these alterations are accompanied by brain metabolic and functional alterations; ii) whether alterations can be modulated through repeated treatment with a drug (naloxone) antagonist to the endogenous μ- and δ-opioid system, and with a drug (antisense oligonucleotide inhibitor of proopiomelanocortin- AS); iii) whether these effects are sex-related; and iv) whether these effects can be reproduced in outbred (CD1) as well as in inbred (DBA/2 and C57Bl/6) mice.

Results

– *Body metabolic pattern*
Body metabolic features in handled male mice are consistently different from control animals, and similar to a type-2 diabetes mellitus pattern (body weight at 90 days of age +7.5%; basal fasting glycaemia +42%; plasma insulin + 125%; corticosterone +110%; ACTH +169%, epididymal fat pads weight – an abdomen obesity sign – +74%).

Conversely, adult female mice do not show consistent hormonal, behavioural and metabolic alterations following neonatal handling.

– *Cerebral excitability*
Following neonatal handling, male DBA/2 showed consistently less epileptiform pattern *versus* controls (polispike-and-waves complexes *per* recording hour, mean 8.5 ± 3.1 *versus* 27.6 ± 6.5, $p < 0.05$; n=6), whereas handled female mice show EEG epileptiform pattern not significantly different from controls.

– *Brain neurophysiology & metabolic pattern*
N1, N2 and N3 peaks of flash-evoked response (VEPs) showed a faster reactivity in manipulated male mice *versus* controls (-9.3%); this corresponded to a different NAD(P)H fluorescence imaging of *ex vivo* isolated brain visual cortex, i.e., +32.3% more elevated deflection of the second part of the curve $\Delta F/F$ (re-charge). Different VEPs effects (to be studied) were found in male and female mice of different strains.

– *Drug effects*
Some parameters, such as body weight, epididymal fat pad (not fasting glycaemia, nor insulinemia), NAD(P)H fluorescence imaging and VEPs were normalized in formerly manipulated and naloxone-treated adult mice, whereas all parameters were drawn to control values in formerly manipulated and AS-treated adult mice.

Conclusions

These results indicate that the onset of sex differences may be very precocious, and that sex is an independent variable for the developmental programming in the brain-body relationship, presumably through the sex-dependent modulation of hypothalamus-pituitary-adrenal feedback mechanisms (bound also to cerebral excitability) following neonatal stressful procedures.

Publications of the project

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Patents

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