Towards a mouse model of depression

a psychoneuroendocrine approach

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“Men ought to know that from the human brain and from the human brain only arise our pleasures, joys, laughter, and jests as well as our sorrows, pains, grief and tears...It is the same thing which makes us mad or delirious, inspires us with dread and fear, whether by night or by day, brings us sleeplessness, inopportune mistakes, aimless anxiety, absent-mindedness and acts that are contrary to habit...”

Hippocrates

Voor Luka,
mijn zoon,
mijn waarheid

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List of Abbreviations

ACTH	adrenocorticotropic hormone
ADX	adrenalectomy
ANOVA	analysis of variance
AVP	arginine vasopressin
CA	cornu ammonis area of the hippocampus
CHB	circular hole board
CORT	corticosterone/cortisol
CRH	corticotrophin releasing hormone
DG	dentate gyrus area of the hippocampus
GLM	general linear model
GR	glucocorticoid receptor
HPA axis	hypothalamic-pituitary-adrenal axis
MIF	Mifepristone or RU38486, GR antagonist
Min	minutes
MR	mineralocorticoid receptor
OD	optical density
PCA	principal component analysis
PVN	hypothalamic paraventricular nucleus
SEM	standard of the mean
VEH	vehicle (=control)
RU	RU38486 (Mifepristone), GR antagonist
WM	water maze

Preface

Stress is an undeniable fact within modern societies. Our 24/7 economy challenge us with increasing social and professional pressures. Already in 2003, the World Health Organization declared “stress” as a major cause of health problems. Prolonged periods of stress that are out of control for the individual can lead to the development of mood disorders like depression. Patients are seriously hampered in day-to-day activities. As a consequence, this costs the society billions in terms of loss of productivity and health assurance costs. Discovery of new drug targets is a necessity.

A fundamental question for the neurobiology of mental health is how adaptation to both acute and chronic stress can become impaired and capable to precipitate emotional and cognitive disturbances characteristic for mood and anxiety disorders. The glucocorticoids, cortisol and corticosterone (CORT), are secreted from the adrenal glands by activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis in response to stress, as well as in a circadian fashion. They are powerful hormonal neuroendocrine mediators of environmental influences on brain and body. Changes in the functionality of this glucocorticoid regulated stress system, supports the general believe that chronic stress leads to an altered hormonal secretion pattern, and is considered a central player in the development of mood disorders. Animal models for stress-related mood disorders are urgently needed for further development of new drugs.

In order to develop an animal model with altered functionality of the glucocorticoid regulated stress system we applied repeated exposure of mice to psychosocial stress, i.e., the presence of a rat. Studying mice in a familiar and novel environment(s) revealed a phenotype characteristic for chronic stress: emotional, cognitive processes were associated with dynamic changes in circadian patterns of neuroendocrine and behavioral activity during, and following the exposure to the chronic psychosocial stressor.

Our experimental designs allowed us to detect a differential contribution of brain systems to memory formation under stress. We found that a change in the sensitivity of the reward system contributes to cognitive impairments, which can be partially normalized by additional reward. Stress induced in mice by the chronic stress paradigm and stress in humans, induced a similar finding namely a shift to more rigid stimulus response learning. This indicates that our animal model can be used to study overlapping brain processes between the two species. The findings open a new perspective for the treatment of stress-related mood disorders like depression.

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