Early life experience : neuroendocrine adaptations to maternal absence

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List of abbreviations

11ß-HSD	11ß-hydroxysteroid dehydrogenase
$5HT_{1A}$	5-hydroxytryptamine (serotonin) 1A
ACTH	adrenocorticotropic hormone
ANOVA	analysis of variance
AVP	vasopressin
BNST	bed nucleus of the stria terminalis
CA	cornu ammonis (part of the hippocampal formation)
CeA	central amygdala
CON	control (mice not separated from their mother)
CRH	corticotropin-releasing hormone
CRHr1	corticotropin-releasing hormone receptor 1
CRP	C-reactive protein
DEP	deprived (pups separated from their mother for 24 hours)
DG	dentate gyrus (part of the hippocampal formation)
GR	glucocorticoid receptor
HPA axis	hypothalamic-pituitary-adrenal axis
IL	interleukin
LG-ABN	licking and grooming - arched back nursing (posture description of the dam for maternal behaviour towards pups)
MC2	melanocortin receptor 2
MR	mineralocorticoid receptor
mRNA	messenger ribonucleic acid
NPY	neuropeptide Y
NSEP	non-separated (undisturbed control mice for SEP treated animals)
O.D.	optical densitiy (quantification of mRNA expression)
PEG	polyethylene glycol
pnd	postnatal day
POMC	pro-opiomelanocortin
pPVTh	praventricular thalamic nucleus
PVN	paraventricular nucleus of the hypothalamus
RIA	radio immunoassay
S.E.M.	standard error of the mean
SEP	separated (pups separated from their mother for 8 hours)
SEP+N	separation procedure combined with novelty exposure
SHRP	stress hypo-responsive period

Glossary

adaptation

Adaptation refers to changes in physiological processes and behavioural performance aimed to restore homeostasis.

desensitisation

The reduction of a biological response to repeated exposures to a substance or stimulus.

habituation

Habituation is an example of non-associative learning, in which there is a progressive diminution of behavioural or physiological response, probability due to repetition of a stimulus. If a sensory stimulus is neither rewarding nor harmful the animal learns (consciously or unconsciously) to suppress its response through repeated encounters. Habituation is stimulus-specific.

Hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is a complex set of direct influences and feedback interactions between the hypothalamus, pituitary and adrenal that are mediated by hormones, *i.e.* CRH and vasopressin released from the hypothalamic paraventricular nucleus (PVN), pro-opiomelanocortin peptides ACTH and ß-endorphin released from pituitary corticotrophs, and corticosterone (rodent, man) and cortisol (man) secreted from the zona fasciculate of the adrenal cortex. The fine, homeostatic interactions between these three organs control reactions to stressors and regulate various body processes, including behavioural adaptation, mood, energy metabolism, immune and inflammatory responses. See also ***section 1.1.1***.

maternal deprivation

A rodent model to mimic and study the effects of adverse early life experiences on development. In this thesis, this model consists of the separation of CD1 mouse pups from their mother for a single episode of 24 hours. See also ***sections 1.4.5*** and ***1.4.6***.

novelty

An experimental procedure, in which an animal is solitarily placed in a new environment. Usually applied to evoke and study glucocorticoid or behavioural stress responses.

repeated maternal separations

A rodent model to mimic and study the consequences of adverse early life experience on development. In the literature usually daily separations of 3-6 hours from birth to weaning are described. In this thesis, this model consists of up to three daily periods of 8 hours of maternal absence at postnatal days 3, 4 and 5. See also ***sections 1.4.3*** and ***1.4.4***.

sensitisation

Sensitisation is an example of non-associative learning, in which the progressive amplification of a response follows repeated administrations of a stimulus.

stress

"A real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioural responses. In biomedical terms, stress often refers to situations in which adrenal glucocorticoids and catecholamines are elevated because of an experience." As defined by BS McEwen (2000) *Brain Research* 886(1-2): 172-189.

stress hypo-responsive period (SHRP)

A critical period during early development in rodents (rats postnatal days 4 to 14, mice postnatal days 1 to 12) for maturation of the HPA axis. This period is characterised by very low and stable circulating basal levels of ACTH and corticosterone. The responsiveness of the pituitary and adrenal to most mild stimuli is strongly reduced. See also ***section 1.3.1***.

List of publications

Enthoven L, Oitzl MS, Koning N, van der Mark M and de Kloet ER(2007) "The pituitary-adrenal axis of the CD1 mouse infant desensitises to repeated maternal separations, but remains highly responsive to stress." *submitted*

Enthoven L, de Kloet ER and Oitzl MS (2007) "Effects of maternal deprivation of CD1 mice on performance in the water maze and swim stress." *submitted*

Dalm S, **Enthoven L**, Meijer OC, van der Mark M, Karssen AM, de Kloet ER and Oitzl MS (2005) "Age-related changes in hypothalamic-pituitary-adrenal axis activity of male C57BL/6J mice." *Neuroendocrinology* 81(6): 372-380

van Overveld PGM, **Enthoven L**, Ricci E, Rossi M, Felicetti L, Jeanpierre M, Winokur ST, Frants RR, Padberg GW and van der Maarel SM (2005) "Variable hypomethylation of D4Z4 in facioscapulohumeral muscular dystrophy." *Annals of Neurology* 58(4): 569-576

Enthoven L, Dalm S, de Kloet ER and Oitzl MS (2004) "Swim posture of mice does not affect performance in the water maze." *Brain Research 'Main Journal'* 1003(1-2): 36-41

Grootendorst J, **Enthoven L**, Dalm S, de Kloet ER and Oitzl MS (2004) "Increased corticosterone secretion and early-onset of cognitive decline in female apolipoprotein E-knockout mice." *Behavioural Brain Research* 148(1-2): 167-177

Schmidt MV, **Enthoven L**, van Woezik JH, Levine S, de Kloet ER and Oitzl MS (2004) "The dynamics of the hypothalamic-pituitary-adrenal axis during maternal deprivation." *Journal of Neuroendocrinology* 16(1): 52-58

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Arbesman S, **Enthoven L** and Monteiro A (2003) "*Ancient Wings*: animating the evolution of butterfly wing patterns." *BioSystems* 71(3): 289-295

Schmidt MV, **Enthoven L**, van der Mark M, Levine S, de Kloet ER and Oitzl MS (2003) "The postnatal development of the hypothalamic-pituitary-adrenal axis in the mouse." *International Journal of Developmental Neuroscience* 21(3): 125-132

Grootendorst J, Oitzl MS, Dalm S, **Enthoven L**, Schachner M, de Kloet ER and Sandi C (2001) "Stress alleviates reduced expression of cell adhesion molecules (NCAM, L1) and deficits in learning and corticosterone regulation of apolipoprotein E knockout mice." *European Journal of Neuroscience* 14(9): 1505-1514

Curriculum Vitae

Leo Enthoven werd geboren op 16 oktober 1976 in de gemeente Amsterdam. Hij haalde zijn atheneum diploma in 1995 aan het Zwijsen College te Veghel. In september van datzelfde jaar begon hij zijn studie biologie aan de Universiteit Leiden, waar hij in 2000 afstudeerde. Tijdens deze studie heeft hij verschillende onderzoeksstages gedaan: een hoofdvakstage van 9 maanden bij Medische Farmacologie (LACDR, LUMC, Universiteit Leiden) onder begeleiding van Dr. M.S. Oitzl en Prof. Dr. E.R. de Kloet, een buitenlandstage van 5 maanden bij Neurobiologie aan het Deutsches Primaten Zentrum in Göttingen, Duitsland onder begeleiding van Dr. E. Isovich en Prof. Dr. E. Fuchs en een nevenstage van 6 maanden bij Evolutiebiologie (EEW, Universiteit Leiden) onder begeleiding van Dr. A. Monteiro en Prof. Dr. P. Brakefield. Aansluitend was hij werkzaam als promovendus bij Medische Farmacologie, onderdeel van het Leiden/Amsterdam Center for Drug Research en het Leids Universitair Medisch Centrum, onder begeleiding van Prof. Dr. E.R. de Kloet en Dr. M.S. Oitzl. Het daar uitgevoerde onderzoek staat beschreven in dit proefschrift. Dit onderzoek was onderdeel van het NDRF-project "Nuclear receptors: novel targets for tissue-specific antidepressants", een samenwerking tussen de Universiteiten van Groningen, Amsterdam en Leiden, het Huybrecht Laboratorium (Utrecht) en Organon N.V. (Oss). Sinds januari 2007 werkt hij als statistisch onderzoeker in de sector Indexcijfers prijzen en conjunctuur, onderdeel van de Divisie Macro-economische Statistieken en Publicaties van het Centraal Bureau voor de Statistiek.

Leo Enthoven was born on October 16th, 1976 in Amsterdam. In 1995 he graduated from high school (atheneum) at Zwijsen College in Veghel. Later that year he started his Biology degree at Leiden University, which he completed in 2000. During his study he performed several internships: a main internship of 9 months at Medical Pharmacology (LACDR, LUMC, Leiden University) under supervision of Dr. M.S. Oitzl and Prof. E.R. de Kloet, an internship of 5 months at Neurobiology at the Deutsches Primaten Zentrum in Göttingen, Germany under supervision of Dr. E. Isovich and Prof. Dr. E. Fuchs, and an internship of 6 months at Evolutionary Biology (EEW, Leiden University) under supervision of Dr. A. Monteiro and Prof. Dr. P. Brakefield. Subsequently, he performed his PhD research at Medical Pharmacology, part of the Leiden/Amsterdam Center for Drug Research and Leiden University Medical Center under the supervision of Prof. Dr. E.R. de Kloet and Dr. M.S. Oitzl. The work from this period is presented in this thesis. This research was part of the NDRF-project "Nuclear receptors: novel targets for tissue-specific antidepressants", a collaboration between the Universities of Groningen, Amsterdam and Leiden, the Huybrecht Laboratory (Utrecht) and Organon N.V. (Oss). Since January 2007 he works as a statistical researcher in the department of Price statistics and short-term indicators, part of the division Macro-economic Statistics and Dissemination of Statistics Netherlands.


Bijzonder project, veel geleerd
Eindelijk klaar, in boekvorm gepresenteerd
Dagen vol experimenten, zelden alleen gezwoegd
Altijd een helpende hand, dat deed me goed
Naast collegae ook vrienden, voor afleiding en plezier
Kan ik nu met trots zeggen: als Dr. sta ik hier
Thesis af!

Leo