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## Early life experience : neuroendocrine adaptations to maternal absence

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**List of abbreviations**

|                   |                                                                                                                 |
|-------------------|-----------------------------------------------------------------------------------------------------------------|
| 11 $\beta$ -HSD   | 11 $\beta$ -hydroxysteroid dehydrogenase                                                                        |
| 5HT <sub>1A</sub> | 5-hydroxytryptamine (serotonin) 1A                                                                              |
| ACTH              | adrenocorticotrophic 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 density (quantification of mRNA expression)                                                             |
| PEG               | polyethylene glycol                                                                                             |
| pnd               | postnatal day                                                                                                   |
| POMC              | pro-opiomelanocortin                                                                                            |
| pPVTh             | paraventricular 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, probably 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  $\beta$ -endorphin released from pituitary corticotrophs, and corticosterone (rodent, man) and cortisol (man) secreted from the zona fasciculata 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*

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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

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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 Statistiek en Publicaties van het Centraal Bureau voor de Statistiek.

Leo Enthoven was born on October 16<sup>th</sup>, 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.





Leo

