Glucocorticoid pulsatility : implications for brain functioning

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Chapter 8

Summary

The HPA axis is one of the major neuroendocrine axes of the body as it controls a plethora of functions in the brain and periphery via its end secretory product, the glucocorticoids cortisol and corticosterone. In mammals including humans, glucocorticoids are characteristically released in approximately hourly hormone bursts by the adrenal gland. These rapid ultradian hormone pulses increase in amplitude, and to a lesser extent in frequency, in anticipation of the active phase providing a circadian pattern of hormone release. Interestingly, pulse amplitude, frequency and phase all seem to be major determinants in the acute response of the HPA axis. It is however not clear how rapid ultradian oscillations contribute to physiology such as target tissue responsiveness of brain and the response to stress. The objective of this thesis is therefore to assess the role of glucocorticoid pulsatile patterns in brain glucocorticoid signalling and the neuroendocrine and behavioural response to stress.

Chapter 2 describes the screening of a panel of GR primary antibodies in order to find the most suitable antibody to study GR nuclear translocation as a potential marker for tissue responsiveness using immunohistochemistry and confocal imaging. Hereto, ADX rats and cultured AtT20 cells were stimulated with a high dose of glucocorticoids. Interestingly, while some antibodies (i.e. BuGR2, H300) were consistent between the two conditions, we found opposing results in GR nuclear translocation patterns for some GR primary antibodies (i.e. M20, P20) between cultured cells and rat CA1 cells. The latter findings were confirmed in another hippocampal cell population, granule dentate gyrus cells. We therefore concluded that findings from cell culture studies cannot always be extrapolated to in vivo situations and that the outcome of antibody-dependent studies can depend heavily on the choice of the antibody. The H300 GR primary antibody consistently demonstrated nuclear translocation patterns in both cultured cells and in brain sections and was therefore chosen to continue further studies.

In **chapter 3** we further characterised receptor nuclear translocation in the rat hippocampus as a potential marker for glucocorticoid signalling. Hereto, both intact and ADX rats were injected with a high dose of corticosterone mimicking the stress response. Subcellular distribution patterns of MR and GR at different time points after injection were measured in single cells in the different hippocampal subfields using the same methodology as chapter 2. We found significant subregion-specific differences in translocation patterns for both MR and GR, with respect to the extent and timing of nuclear translocation. Moreover, specific differences between ADX and intact animals that are most prominent in the dentate gyrus. We conclude that in response to a single stress-like increase in corticosterone distinct region-specific MR and GR-dependent translocation patterns exist in the rat hippocampus.

The effects of long-term disturbances in endogenous corticosterone pulsatile patterns on molecular markers for target tissue sensitivity to an additional glucocorticoid challenge mimicking the stress response are described in **chapter 4**. Diurnal and ultradian corticosterone fluctuations were clamped at constant levels in intact animals by exogenous administration of corticosterone by means of subcutaneous corticosterone pellet implantation. Additionally, recovery from constant exposure was studied in groups that had the pellet removed 24 hours prior to the challenge. Molecular markers for receptor responsiveness to this acute challenge were examined in the rat hippocampal area. The constant exposure to the steroid resulted in dose-dependent down-regulation of GR and attenuated MR and GR translocation to the acute challenge. Interestingly, while glucocorticoid responsive expression of Gilz to the challenge was already attenuated during stable daily average levels (40%), resistance of Sgk-1 gene expression to the challenge was only observed after constant high corticosterone exposure (100%). Washout of 100% cort recovered all molecular markers (partial) while removal of the 40% cort pellet still attenuated responsiveness to the challenge. This finding suggests differential responsiveness of the two genes due to treatment. Using these molecular markers we conclude that tissue responsiveness to glucocorticoids is maintained by pulsatile rather than constant exposure to the hormone.

In **chapter 5** flattening of ultradian and circadian glucocorticoid pulsatility via subcutaneous pellet implantation was verified and validated by high frequency automated blood sampling with 10 min intervals. Corticosterone rhythms were effectively flattened around daily average (40%) or at levels seen during stress-related disease (100% cort). Removal of the corticosterone pellet resulted in rapid recovery of ultradian pulsatility in the 40% group but not in the 100% group, most likely due to a local depot formation in the skin. However, we found a dissociation between neuroendocrine and behavioural responsiveness to noise stress. Animals previously exposed to 40% corticosterone showed less and shorter behavioural activity to noise stress compared to 100% corticosterone and vehicle treated animals while their endocrine response was similar to vehicle animals. This data suggest that even though HPA axis activity adjusts in a reversible fashion to alterations in the characteristic pulsatile pattern of corticosterone, this happens in spite of longer lasting changes in the brain affecting stress responsiveness.

Chapter 6 describes the neuroendocrine and behavioural response to stress in relation to ultradian corticosterone pulses. We have addressed this question by infusing identical amounts of corticosterone but in constant or hourly pulsatile patterns in ADX rats. We also varied the pulse amplitude without altering total administered dose by adjusting both the concentration and duration of infused corticosterone. At the end of infusion – and either during the rising or falling phase of our exogenous pulse – animals were exposed to 10 minutes of 99 dB noise stress. Constant administration of corticosterone resulted in a blunted ACTH response to stress, while pulsatile administration facilitated a brisker response

markedly greater in the rising than in the falling phase of a corticosterone pulse. This differential phase-dependent effect was also seen in the behavioural response to noise which was much greater in the rising phase. Interestingly, we found strong region-specific differences in c-fos neuronal expression patterns as a function of either pulse amplitude or phase, indicating that under stress different brain circuits are differentially affected by glucocorticoid pulsatility. We conclude that the current data provide strong evidence for pattern-dependent stress responsivity in which different brain circuits show differential sensitivity to the phase and amplitude of pulsatile corticosterone exposure.

As discussed in **chapter 7**, a new concept in the endocrinology of glucocorticoids has evolved from the data presented in this thesis showing that pulsatile release of glucocorticoids is a major determinant in 'resilience' of glucocorticoid signalling and stress responsiveness. Moreover, we have revealed that in particular the GR is affected when glucocorticoid pulsatility is disrupted and could thus provide a excellent target for therapy to normalise the downstream effects of disturbances in glucocorticoid rhythms in stress-related disease. Potential mechanisms and suggestions for future research are extensively discussed in the general discussion.

Samenvatting

Stress, zowel fysiek als psychisch, zorgt voor snelle fysiologische veranderingen in het lichaam. Activering van het sympathische zenuwstelsel resulteert via adrenaline en noradrenaline in o.a. een verhoogde hartfrequentie, bloeddruk en bloedtoevoer naar de spieren. Dit stelt een individu in staat om vrijwel direct en adequaat op de situatie te reageren. Daarnaast zorgt activering van de hypofyse-bijnier as [in het Engels: hypothalamic-pituitary-adrenal (HPA) axis] voor acute afgifte van de glucocorticoïd stresshormonen (cortisol bij de mens, corticosteron bij knaagdieren). Deze hormonen zijn essentieel in het vrijmaken van beschikbare energie voor de reactie op stress maar controleren ook een overvloed aan functies in de periferie en de hersenen zoals cognitie, emotie en perceptie. De acties van glucocorticoïden worden gemedieerd via twee receptoren, de mineralocorticoïd en de glucocorticoïd receptor (MR en GR), die samen HPA-as activiteit handhaven. MR wordt geacht tonische HPA-as activiteit en de drempel van het systeem te reguleren ('pro-actieve' modus), terwijl GR het herstel van stress te bevordert ('reactieve' modus).

Het is recentelijk beschreven dat vrijwel alle hormonen in het lichaam, inclusief de glucocorticoïden, worden afgegeven volgens een bepaald pulsatiel patroon. Dit is het ultradiane ritme en zorgt voor de uurlijkse afgifte van glucocorticoïden door de bijnier in alle zoogdieren, waaronder de mens. Het circadiane ritme dat onder invloed van de biologische klok in de hersenen staat superponeerd hier dag/nacht fluctuaties op. Het circadiane en ultradiane ritme werken nauwgezet samen om zo intrinsieke ritmiciteit van de HPA-as te controleren vanwege de grote invloed op onder andere gezondheid, vitaliteit en het immuunsysteem.

Het is op het moment bekend dat tijdens chronische stress of ziekte de vatbaarheid voor stress-gerelateerde en autoimmuunziekten toeneemt. Bovendien zijn stoornissen in het karakteristieke pulsatiele patroon van glucocorticoïd afgifte vaak beschreven in stress-gerelateerde pathologie. Het is echter niet duidelijk hoe snelle ultradiane oscillaties in glucocorticoid niveaus bijdragen aan fysiologie, stress responsiviteit en receptor signalering in het brein. Het doel van het beschreven onderzoek in dit proefschrift is daarom gericht op de rol van glucocorticoïd pulsatiele patronen op glucocorticoïd signalering in de hersenen, HPA-as activiteit en de neuroendocriene en gedragsrespons op stress.

Hoofdstuk 2 beschrijft een studie waarin wordt gezocht naar het meest geschikte antilichaam om het proces van GR nucleaire translocatie te visualiseren als mogelijke marker voor weefsel responsiviteit. Met behulp van immunohistochemische technieken en confocale microscopie werd een panel van GR primaire antilichamen getest in zowel een cellijn als hersenweefsel. Om nucleaire translocatie van GR te induceren zijn bijnierloze ratten en AtT20 cellen gestimuleerd met een hoge dosering glucocorticoïd. Het blijkt dat hoewel

sommige antilichamen (bijv BuGR2 en H300) overeenstemmende resultaten vertonen tussen de twee condities, we tegenstrijdige resultaten in translocatiepatronen tussen gekweekte cellen en rat hippocampale CA1 cellen met andere GR antilichamen vinden (bijv M20, P20). De laatste bevindingen werden ook bevestigd in granulaire dentate gyrus cellen, een andere hippocampale celpopulatie. Wij concluderen dat de bevindingen in cellijnen niet altijd kunnen worden geëxtrapoleerd naar de in vivo situatie en dat de uitkomst van antilichaamafhankelijke onderzoeken sterk kan afhangen van de keuze van het antilichaam. Aangezien de GR H300 antilichaam consistent nucleaire translocatie patronen in zowel gekweekte cellen als in hersenen secties heeft aangetoond werd deze gekozen om verdere studies voort te zetten.

In **hoofdstuk 3** hebben we receptor nucleaire translocatie in de hippocampus van ratten als een mogelijke marker voor glucocorticoïd signalering verder gekarakteriseerd. Zowel intacte als bijnierloze ratten zijn geïnjecteerd met een hoge dosis corticosteron om de stressrespons na te bootsen. Vervolgens is met dezelfde methode als beschreven in hoofdstuk 2 de subcellulaire localisatie van MR en GR op verschillende tijdstippen na injectie gemeten in verschillende subgebieden van de hippocampus. We hebben significante subregio-specifieke verschillen in de translocatiepatronen voor zowel MR en GR gevonden met betrekking tot de omvang en de timing van de nucleaire translocatie. Bovendien waren de specifieke verschillen tussen intacte en bijnierloze dieren het meest prominent in de gyrus dentatus. We concluderen dat in reactie op een met stress vergelijkbare stijging in corticosteron niveaus er regio-specifieke verschillen in MR en GR translocatie patronen bestaan in de hippocampus van ratten.

De effecten van langdurige verstoringen in glucocorticoïd pulsatiele patronen op moleculaire markers voor weefselgevoeligheid worden beschreven in **hoofdstuk 4**. Exogene toediening door middel van subcutane corticosteron pellet implantatie werd gebruikt om zowel circadiane als ultradiane corticosteron fluctuaties op een constant niveau in intacte dieren vast te 'klemmen'. Om stressachtige weefselresponsen te induceren werden alle dieren na een week geïnjecteerd met een extra dosering glucocorticoïd. Eventueel herstel van constante blootstelling werd onderzocht in groepen waarin 24 uur voorafgaand aan de extra injectie de corticosteron pellet was verwijderd. Vervolgens zijn verschillende moleculaire markers voor receptor functie onderzocht in de hippocampus van de rat. Constante blootstelling aan de steroïden resulteerde in een dosis-afhankelijke vermindering van GR niveaus en resistentie in MR en GR translocatie na de acute injectie. Interessant is dat constante blootstelling aan dagelijks gemiddelde niveaus (40%) de glucocorticoïd-afhankelijke inductie van target gen Gilz al verminderde, terwijl de expressie van Sgk-1 alleen werd beïnvloed na blootstelling aan constante hoge corticosteron niveaus (100%). Deze bevinding suggereert gen-specifieke verschillen in glucocorticoid responsiviteit, afhankelijk van het patroon van corticosteron toediening. Het uitwassen van hoge concentraties resulteerde verder in vrijwel

volledige normalisatie van alle moleculaire markers, terwijl 24 uur na het verwijderen van de 40% cort pellet weefsel responsiviteit nog steeds aangedaan was. Met behulp van deze moleculaire markers concluderen we dat de flexibiliteit in weefselreactiviteit op glucocorticoïden wordt onderhouden door pulsatiele in plaats van voortdurende blootstelling aan het hormoon.

In **hoofdstuk 5** is met behulp van een geautomatiseerd bloedafnamesysteem met hoog frequente intervallen (elke 10 minuten) het afplatten van ultradiane en circadiane glucocorticoïd pulsatiliteit via subcutane pellet implantatie gecontroleerd en gevalideerd. Uit de resultaten blijkt dat na beide manipulaties corticosteron ritmes inderdaad effectief zijn afgeplat rond het dagelijks gemiddelde (40% cort) of op een niveau vergelijkbaar met stress-gerelateerde ziekte (100% cort). Verwijdering van de corticosteron pellet resulteerde in een snel herstel van ultradiane pulsatiliteit in de 40% groep, maar niet in de 100% groep. Dit laatste is waarschijnlijk te wijten aan de formatie van een lokaal depot in de huid. Interessant genoeg vonden we een dissociatie tussen de neuroendocriene en gedragsreactie op geluidstress 24 uur na verwijdering van de pellet. Dieren blootgesteld aan 40% corticosteron vertonen verminderde en verkorte reactiviteit op geluidstress in vergelijking met 100% corticosteron en controle dieren, terwijl hun endocriene respons vergelijkbaar was met de controle dieren. Deze gegevens wijzen erop dat hoewel HPA- as activiteit flexibel omgaat met veranderingen in het karakteristieke pulsatiele patroon van corticosteron, dit gepaard gaat met langer durende veranderingen in de hersenen die de gedragsmatige stress responsiviteit bepalen.

Hoofdstuk 6 beschrijft de relatie tussen ultradiane corticosteron pulsen en de neuroendocriene en gedragsreactie op stress. Hiertoe zijn bijnierloze ratten geïnfuseerd met gelijke hoeveelheden corticosteron, maar in óf constant, óf uurlijkse pulsatiele patronen. Door aanpassing van zowel de concentratie en de duur van corticosteron-infusie hebben we ook gevarieerd in de amplitude van de puls, zonder de totale toegediende dosis te wijzigen. Aan het einde van de infusie - en zowel tijdens de stijgende of dalende fase van een uurlijkse puls – werden de dieren blootgesteld aan 10 minuten 99 dB geluidstress. Constante toediening van corticosteron resulteerde in een afgeplatte ACTH respons op stress, terwijl pulsatiele administratie resulteerde in een aanzienlijk grotere respons die meer prominent was tijdens de stijgende dan in de dalende fase van een corticosteron puls. Dit fase-afhankelijke effect hebben we ook waargenomen in de gedragsreactie op geluidsstress. Verder hebben we sterke regio-specifieke verschillen in c-fos neuronale expressie patronen als functie van pulsamplitude of fase gevonden, waaruit blijkt dat onder stress de hersenen verschillende circuits differentieel worden beïnvloed door glucocorticoïd pulsatiliteit. De huidige gegevens verstrekken sterk bewijs voor patroon-afhankelijke stress responsiviteit in de hersenen waarin verschillende circuits differentiële gevoeligheid tonen voor de fase en amplitude van pulsatiele corticosteron blootstelling.

Het functioneren van het stress systeem onder invloed van de pulsatiele afgifte van glucocorticoïd stress hormoon is nog niet eerder onderzocht. In de fysiologie staat hormoon pulsatiliteit centraal en kan een grote rol spelen bij ziekte. Kennis over het functioneren van dit systeem en begrip van de celprocessen in het brein kan dus van groot belang zijn voor het gericht ontwikkelen van nieuwe farmaca en therapieën voor het behandelen van stress-gerelateerde ziekten zoals bijvoorbeeld depressie. Zoals uitvoerig besproken in **hoofdstuk 7** dragen de resultaten van dit proefschrift bij aan een nieuw concept in de neuroendocrinologie van glucocorticoïd stresshormonen. Pulsatiele blootstelling aan glucocorticoïden blijkt een belangrijke factor in de 'veerkracht' van glucocorticoïd signalering en stress reactiviteit. Verder hebben we aangetoond dat met name de GR wordt beïnvloed wanneer glucocorticoïd pulsatiliteit is verstoord. Dit eiwit zou dus uitstekend als doelwit kunnen functioneren voor therapie en normalisatie van de downstream effecten van stoornissen in glucocorticoïd pulsatiele patronen in stress-gerelateerde ziekten. Mogelijke mechanismen en suggesties voor toekomstig onderzoek worden uitvoerig besproken in de algemene discussie van dit proefschrift.

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Oral presentations

Leiden / Amsterdam Center for Drug Research (LACDR) Spring Symposium. April 13, 2010, Amsterdam. Title: Disrupted glucocorticoid pulsatility affects glucocorticoid signalling in the rat brain.

Dutch Endocrine Meeting, January 30, 2010, Noordwijk. Title: Disrupted glucocorticoid pulsatility affects glucocorticoid signalling in the rat brain.

Marius Tausk Masterclass with prof. dr. J. Cidlowski. November 5, 2009, Leiden. Title: Selective brain responses to amplitude and phase of glucocorticoid pulses

Leiden Center for Translational Neuroscience (LCTN) Symposium, October 15, 2009, Leiden. Title: Disrupted glucocorticoid pulsatility affects glucocorticoid signalling in the rat brain.

7th Dutch Endo-Neuro-Psycho meeting. June 4, 2008, Doorwerth. Title: Tissue responsiveness to chronically elevated levels of glucocorticoids: nuclear dynamics of MR and GR in the rat brain.

IRTG Summerschool "Psychobiology of stress: steroid hormone action". June 9, 2008, Leiden. Title: Tissue responsiveness to chronically elevated levels of glucocorticoids: nuclear dynamics of MR and GR in the rat brain.

6th Dutch Endo-Neuro-Psycho meeting. June 6, 2007, Doorwerth. Title: Dynamics of nuclear receptor activation: Mineralocorticoid & Glucocorticoid receptors

Annual meeting of the Physiological Society. December 6, 2006. Title: Different translocation patterns of MR and GR in rat hippocampal subfields

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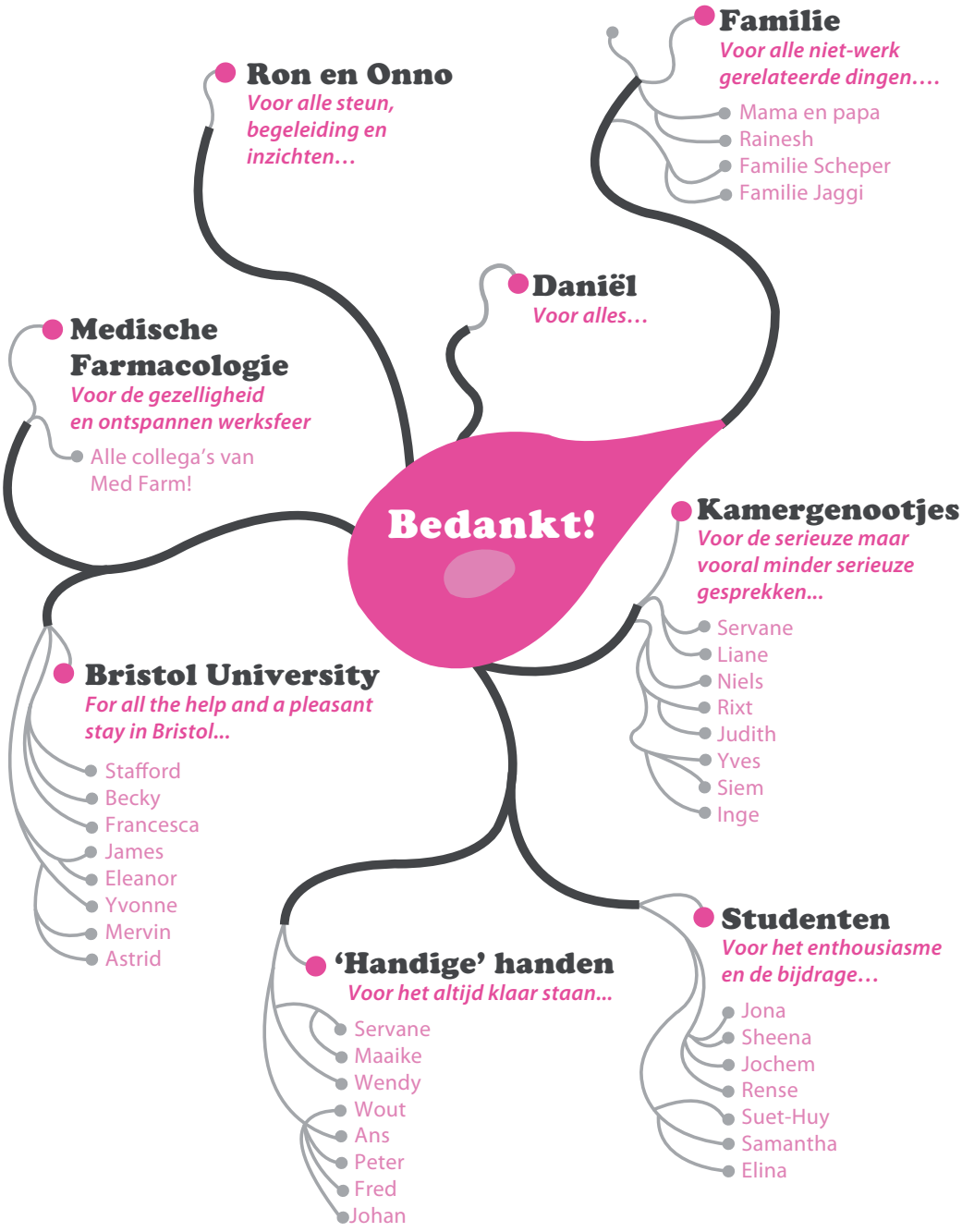

Soms heb je van die dromen die je wakker houden…
tot je ze uitvoert
Loesje