Brain circuitries in control of feeding behaviors

Focus on Neuropeptide Y

Gumbs, M.C.R.

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Appendices.

I. Dutch summary / Nederlandse samenvatting
II. Dose response for NPY1R and NPY5R antagonist doses
III. PhD portfolio, publications, author affiliations

Appendix I. Dutch summary / Nederlandse samenvatting

De prevalentie van obesitas is de afgelopen decennia enorm toegenomen. In 2018, had 50% van de Nederlandse volwassenen overgewicht, waarvan 15% obesitas (RIVM, 2019). Obesitas vergroot het risico op het krijgen van andere ernstige ziekten zoals kanker, of hart- en vaatziekten. Daarom is het belangrijk dat er onderzoek wordt gedaan om een goed werkende therapie te ontwikkelen. Eén van de belangrijkste oorzaken voor het ontwikkelen van obesitas is de consumptie van het moderne dieet met een hoog gehalte aan (verzadigde) vetten en suikers. Een dergelijk dieet brengt veranderingen in de hersenen teweeg, waardoor het makkelijk is om te overeten. In dit proefschrift is met het vet-suikerrijke keuzedieet een dergelijke voedselomgeving nagebootst voor ratten. Zij krijgen onbeperkt toegang tot gewoon rattenvoer ("chow"; dat voornamelijk uit koolhydraten en eiwit bestaat) en een fles met water, maar ook tot lekkere en calorierijke dieetcomponenten zoals een fles met suikerwater en een bakje met vet. Inname van dit dieet leidt bij ratten tot veranderingen die ook bij mensen met obesitas worden gezien, bijvoorbeeld overeten, een toename in vetpercentage en tekenen van diabetes.

De hersenen spelen een belangrijke rol in het reguleren van de energiebalans door het afstemmen van de opgenomen energie uit voeding met de verbruikte energie voor allerlei processen (zoals metabolisme of beweging). De neurale circuits in de hersenen worden vaak ingedeeld in homeostatische- en beloningscircuits. De homeostatische circuits bestaan uit gebieden in de hypothalamus en de hersenstam die deels dicht bij een incomplete bloed-hersenbarrière liggen en zo toegang hebben tot signalen in de circulatie over de energetische status van het organisme. Deze gebieden bewerkstelligen de homeostase in de energiebalans. Het belangrijkste beloningscircuit is het circuit dat betrokken is bij motivatie. Het bestaat uit het ventrale tegmentum ("ventral tegmental area"; VTA) dat projecteert naar de nucleus accumbens (NAc). De beloningscircuits liggen dieper in de hersenen en regelen juist meer de belonende aspecten van (lekkere) voedselinname en helpen bepalen of we iets lekker vinden. Het eiwit Neuropeptide Y (NPY) speelt in beide typen circuits een rol door het verhogen van voedselinname en het verhogen van de motivatie om voedsel te verkrijgen.

In dit proefschrift is met behulp van literatuuronderzoek en dierexperimenten onderzocht hoe veranderingen in de samenstelling van het dieet veranderingen kunnen veroorzaken in NPY in verschillende hersengebieden. Met anatomische studies is ook onderzocht waar in het brein de oorsprong van NPY in het beloningscircuit is. Daarnaast is onderzocht hoe deze circuits zich aanpassen na veranderingen in het dieet, bijvoorbeeld na een korte periode van vasten of juist overeten zoals bij het fcHFHS dieet.

Gevolgen van de dieetsamenstelling op NPY-genexpressie in homeostatische en beloningsgebieden

In **hoofdstuk II** is er onderzocht hoe verschillende diëten kunnen leiden tot veranderingen in de hoeveelheid NPY-eiwit en de genexpressie van *Npy* in homeostatische en beloningsgebieden. Consumptie van koolhydraatrijke diëten leidt over het algemeen tot meer NPY in twee kernen van de hypothalamus: de arcuate nucleus (Arc) en de paraventriculaire nucleus (PVN). Terwijl consumptie van vetrijke diëten juist leidt tot minder NPY in deze kernen. De Arc bevat NPY-cellen die gevoelig zijn voor hormonen en metabolieten in de circulatie en geven dit signaal onder andere door aan de PVN via neuronale projecties. Met name de Arc->PVN projecties zijn heel belangrijk voor de effecten van NPY op voedselinname en veel onderzocht. Dieet kan dus via NPY in deze hersengebieden de regulatie van voedselinname veranderen. Opvallend was dat dieren die toegang hadden tot een vet-suikerrijk keuze dieet verhoogde *Npy* in de Arc hadden na één week consumptie van het dieet. Dit suggereerde dat deze dieren zouden blijven overeten, en dat is ook zo. Na vier weken consumptie lieten deze dieren weliswaar Arc *Npy* niveaus zien die vergelijkbaar waren met de controlegroep, maar vertoonden ze een verhoogde response op een NPY-infusie in de hersenen. Het NPY-systeem was dus gevoeliger geworden. Uit het literatuuronderzoek bleek tevens dat de effecten van dieet consumptie op NPY-niveaus in de beloningsgebieden niet was gemeten in dieren op een vet-suikerrijk keuze dieet. Ook waren de niveaus van de NPY-receptoren (NPY1R, NPY2R, NPY4R en NPY5R) niet gemeten, terwijl dit een aanwijzing zou kunnen zijn naar het mechanisme van de verhoogde gevoeligheid. Daarom zijn in **hoofdstuk III** de genexpressie niveaus gemeten van *Npy*, *Npy1r*, *Npy2r*, *Npy4r*, en *Npy5r* na zes weken consumptie van het vet-suikerrijke dieet in vier hersengebieden; de Arc ter controle, de laterale hypothalamus (LHA) omdat NPY-infusie hier één van de grootste effecten op voedselinname heeft, en in de twee belangrijkste beloningsgebieden, de VTA en de NAc. Consumptie van het vet-suikerrijke dieet leidde alleen in de LHA en NAc tot veranderingen. In de LHA was de *Npy* expressie verhoogd en in de NAc was de *Npy1r* expressie anders gereguleerd over de dag. Dit betekent dat mogelijke veranderingen in receptoren die de verhoogde gevoeligheid voor NPY zouden kunnen verklaren waarschijnlijk op eiwitniveau moeten worden gezocht.

Gezien er weinig bekend was over de regulatie van de NPY-systemen in de LHA en de beloningsgebieden, is in **hoofdstuk IV** onderzocht of 24 uur vasten, wat NPY-niveaus in de Arc verhoogt, ook effect heeft op de NPY-niveaus in de LHA, VTA en NAc. Ook was nog niet bekend wat het effect van vasten op de NPYR-niveaus was in deze gebieden. Onze studie laat zien dat in de Arc *Npy*-niveaus inderdaad stijgen tijdens het vasten en dat Arc *Npy1r*-niveaus dalen door vasten als dit in de lichtperiode wordt gemeten. Wanneer dit in de donkerperiode wordt gemeten, is er na het vasten echter alleen een daling van Arc *Npy2r*-niveaus te zien. Tevens vonden we dat vasten geen effect heeft op *Npy*- of *Npyr*-niveaus in de LHA, of beide

hedonische gebieden, wat betekent dat het NPY-systeem in deze gebieden een andere rol heeft dan in de Arc.

Het effect van NPY-infusie op voedselkeuze hangt af van het hersengebied en de dieetsamenstelling

In een voorgaande studie van onze onderzoeksgroep leidde een intracerebroventriculaire NPY-infusie tot verhoogde inname van chow, maar ook van vet in ratten op het vet-suikerrijke keuze dieet. In de literatuur waren er aanwijzingen dat de regulatie van de voedselkeuze na NPY-infusie verschillend is per hersengebied. Specifiek hadden studies aangetoond dat de NAc belangrijk kan zijn voor het reguleren van de vetinname. Daarom is eerst in **hoofdstuk V** onderzocht of de toename van vetinname kon worden verklaard door NPY-signalering in de NAc. Inderdaad verhogen ratten op het vet-suikerrijke keuze dieet specifiek de vetinname na NPY-infusie in de NAc. Ook toonde deze studie aan dat de NPY1R deze effecten medieert doordat de toename in vetinname geblokkeerd was als er eerst een NPY1R-antagonist werd geïnfundeerd voor de NPY-infusie. Vervolgens hebben wij in **hoofdstuk VI** onderzocht of de NPY-signalering in de LHA zou kunnen bijdragen aan de toename van chow-inname na NPY-infusie. NPY-infusie in de LHA leidt namelijk tot één van de grootste toenames in voedselinname vergeleken met andere hersengebieden. Ratten op het vet-suikerrijke keuze dieet verhoogden inderdaad specifiek de inname van chow na infusie van NPY. Ook hebben wij ontdekt dat het NPY-systeem in de LHA van ratten op het keuze dieet anders werkt dan dat van ratten op een standaard chow dieet. In ratten op het chow dieet kan het NPY-effect namelijk geblokkeerd worden met een pre-infusie van een NPY1R-antagonist of een NPY5R-antagonist. In ratten op het vet-suikerrijke keuze dieet wordt het NPY-effect alleen nog geblokkeerd met een pre-infusie van een NPY5R-antagonist, en niet met een pre-infusie van een NPY1R-antagonist. In de literatuur was aangetoond dat het effect van NPY op voedselkeuze in de PVN, een andere homeostatisch gebied, afhankelijk is van de samenstelling van de basale inname. Daarom hebben wij in **hoofdstuk VII** onderzocht of het effect van NPY in de LHA op voedselkeuze ook afhankelijk is van de samenstelling van de basale inname. Ratten hadden hiervoor de toegang tot het standaard chow dieet, het vet-suikerrijke keuze dieet, of tot een vrije-keuze dieet met maar één van de lekkere componenten; een vetrijk keuze dieet of een suikerrijk keuze dieet.

De effecten van NPY waren inderdaad afhankelijk van de samenstelling van de basale inname. Ratten op het standaard chow dieet, het vet-suikerrijke keuze dieet of het vetrijke dieet verhoogden specifiek de inname van chow. Wanneer rekening gehouden werd met de variatie die de dieren op het vet-suikerrijke keuze dieet vertoonden in hun basale inname, vonden we dat dieren met een hoge vet::suiker ratio (gelijke basale inname van vet en suiker) ook de vetinname verhoogden na NPY-infusie. Dieren op het vet-suikerrijke keuze dieet die een lage vet::suiker ratio hadden (lage basale inname van vet, en een relatief hoge inname

van suiker) verhoogden echter alleen de chow-inname. Opvallend was dat dieren die het suikerrijke keuze dieet consumeerden, ongevoelig waren geworden voor de NPY-infusie. Inname van weinig vet met veel suiker of juist alleen veel suiker verandert dus het NPY-systeem in de LHA zodanig dat het, respectievelijk, ook de inname van lekkere dieetcomponenten stimuleert of juist ongevoelig(er) wordt. Gezamenlijk tonen de studies in hoofdstuk V, VI en VII aan dat de effecten van NPY op voedselinname afhankelijk zijn van het hersengebied en de basale samenstelling van het geconsumeerde dieet.

De oorsprong van NPY in de beloningsgebieden

NPY is in veel hersengebieden aanwezig in neuronen. Daarnaast kan NPY ook via de axonen van een neuron worden afgegeven in andere hersengebieden. NPY is voornamelijk in de homeostatische gebieden onderzocht; de projectie van de Arc naar de PVN is het meest onderzocht en speelt een belangrijke rol in de regulatie van voedselinname. De Arc NPY neuronen projecteren echter ook naar de LHA en er bestaan ook NPY-projecties vanuit het C1/A1 gebied in de hersenstam naar de PVN. De oorsprong van NPY in de beloningsgebieden is echter minder bekend. In de NAc zijn wel lokale neuronen aanwezig die NPY tot expressie brengen, maar het was onbekend of er ook een NPY-projectie naar de NAc is. In **hoofdstuk V** is met een retrograde tracer gevonden dat de Arc NPY-neuronen ook naar de NAc projecteren. De literatuur was inconsistent over de aanwezigheid van NPY-neuronen in de VTA. In **hoofdstuk VIII** is door systematisch onderzoek aangetoond dat er geen NPY-neuronen in de VTA aanwezig zijn onder normale fysiologische omstandigheden in mannelijke ratten. Wel projecteren de Arc en de C1/A1 NPY-neuronen naar de VTA. Beide beloningsgebieden kunnen dus direct een NPY-signaal uit de homeostatische gebieden ontvangen.

Effecten van vasten op de beloningssystemen

In **hoofdstuk IX** hebben we onderzocht of een korte periode van vasten de genexpressie van genen uit het dopamine- of opioïde-systeem kan moduleren. Het dopamine systeem reageert namelijk op hormonen die betrokken zijn bij de regulatie van voedselinname. Deze hormonen signaleren via G-gekoppelde eiwitten, wat een indicatie is dat de genexpressie ook wordt beïnvloed. De dopamine- en opioïde systemen reguleren andere aspecten van beloning. Het dopamine systeem reguleert de motivationele aspecten (‘wanting’) terwijl het opioïde systeem de belonende aspecten (‘liking’) reguleert. Wij vonden dat vasten voornamelijk resulteerde in veranderingen in dopaminerge genexpressie en alleen in de VTA, de oorsprong van mesolimbische dopamine neuronen. In de VTA was de genexpressie voor de dopamine 2 receptor en het tyrosine hydroxylase enzym (wat nodig is om dopamine te maken) verlaagd op een tijdstip wanneer de ratten normaal zouden voorbereiden op het ontvangen van een maaltijd. Dit zou kunnen betekenen dat er op dat moment minder dopamine vrij komt.

Effecten van dieetsamenstelling op het beloningssysteem

Het beloningssysteem is anders in mensen met obesitas dan in slanke mensen. Dopamine 2 receptor (DRD_2) binding is bijvoorbeeld verlaagd in het striatum (waarvan de NAc een onderdeel is), wat een indicatie kan zijn dat de DRD_2 daar minder tot expressie komt in mensen met obesitas. Eerdere studies in onze onderzoeksgroep hadden aangetoond dat de dieetsamenstelling van invloed is op de hoeveelheid beschikbare $DRD_{2/3}$ in het ventrale striatum. Ook kon de basale inname van vet in verband worden gebracht met de hoeveelheid $DRD_{2/3}$ in het striatum en de response van ratten op een amfetamine injectie. Om de $DRD_{2/3}$ te meten, moet de rat echter geofferd worden. In **hoofdstuk X** hebben we onderzocht of de reactie op een amfetamine injectie voorspellend is voor de hoeveelheid $DRD_{2/3}$ in verschillende delen van het striatum zodat de bepaling van de hoeveelheid beschikbare $DRD_{2/3}$ niet *post mortem* hoeft plaats te vinden. In ratten op een standaard chow dieet voorspelde de amfetamine reactie de hoeveelheid beschikbare $DRD_{2/3}$. In ratten op een vet-suikerrijk keuze dieet echter niet, terwijl in beide groepen geen verschil was gemeten in de hoeveelheid $DRD_{2/3}$. Voorlopig kan de amfetamine injectie dus alleen als voorspeller van $DRD_{2/3}$ beschikbaarheid gelden in ratten op een standaard chow dieet.

Conclusies

In de bovenstaande studies hebben wij een aantal fundamentele bevindingen gedaan over het functioneren en de organisatie van het centrale NPY-systeem. NPY signaleert via de NPY1R in de NAc om vetinname te stimuleren, en via de NPY1R en NPY5R in de LHA om de inname van complexe koolhydraten te stimuleren. De oorsprong van NPY in de NAc is een lokale bron alsook een projectie vanuit de Arc NPY-neuronen. In de VTA komt NPY juist vanuit twee projecties; de Arc NPY-neuronen en NPY-neuronen in de C1/A1 gebieden van de hersenstam. Daarnaast concluderen we dat het consumeren van voedsel dat veel vet en suiker bevat, kan leiden tot veranderingen in het LHA NPY systeem van de homeostatische circuits en in het dopamine systeem van de beloningscircuits.

Appendix II. Dose response for the NPY1R-antagonist and NPY5R-antagonist in the nucleus accumbens and lateral hypothalamic area

Attachment to chapter VI (M.C.R. Gumbs et al., *accepted*).

Obesity prevalence has tripled over the past 40 years, which can be attributed for a great part to the consumption of energy-rich, palatable diets, which lead to a dysregulation of the regulatory systems of energy balance. Neuropeptide Y (NPY) is a potent orexigenic peptide that exerts its effects via four NPY receptors; NPY1R, NPY2R, NPY4R, and NPY5R. In models of diet-induced obesity (DIO), it has been found that the central NPY system is dysregulated (M. C. Gumbs et al., 2016; Hansen et al., 2004; van den Heuvel, Eggels, van Rozen, et al., 2014; Widdowson et al., 1997). In addition, we have determined that NPY has region-specific effects on food intake. In our free-choice high-fat high-sugar (fcHFHS) DIO model, NPY infusion into the nucleus accumbens (NAc) of the reward system leads to increased intake of fat (van den Heuvel et al., 2015), whereas infusion into the lateral hypothalamic area (LHA) leads to intake of chow (M.C.R. Gumbs et al., *accepted*). To be able to determine which NPY receptor underlies the effects of NPY infusion on intake in these regions, a pharmacological approach was devised in which NPY receptor-specific antagonists were infused prior to NPY infusion, and food intake was measured subsequently. The aim of our dose response studies was to find an antagonist dose that did not affect food intake by itself to determine the effects of NPY receptor blockade on NPY-induced feeding.

In our dose response studies, fcHFHS- and CHOW-fed control animals were implanted with bilateral cannulas aimed at the NAc or the LHA. In three different dose response experiments, the effect of different doses of NPY1R-antagonist (GR231118, also known as GW1229 or 1229U91) or NPY5R-antagonist (L-152,804) were infused at the beginning of the dark period when hypothalamic NPY levels are high (Akabayashi et al., 1994; Jhanwar-Uniyal et al., 1990; McKibbin et al., 1991). Food intake was measured two and four hours later. For the NAc, only GR231118 was tested. For the LHA, both GR231118 and L-152,804 were tested.

Experimental procedures

Animals and housing

All experiments were performed with adult male Wistar rats (Charles River Breeding Laboratories, Sulzfeld, Germany) weighing 270-300 grams at arrival. Rats were housed in temperature- (21 ± 2 ˚C), humidity- (60 ± 5 %) and light-controlled (12:12hr light/dark; lights on 07:00-19:00) rooms with background noise (radio) during the entire experiment. Rats had *ad libitum* access to a container with a standard high-carbohydrate diet (Teklad global diet 2918; 24% protein, 58% carbohydrate, and 18% fat, 3.1 kcal/g, Envigo, Horst, The

Netherlands) and a bottle of tap water. The animal ethics committees of the Amsterdam UMC of the University of Amsterdam and The Netherlands Institute for Neuroscience approved all experiments according to Dutch legal ethical guidelines.

Stereotactic surgery

The reader is referred to chapter VI for details on stereotactic surgery and diet intervention. Briefly, animals were anesthetized and implanted with bilateral cannulas aimed at the lateral hypothalamus for infusions using a stereotactic frame. Cannula's were placed in an angle of 10° in the frontal plane. For the LHA, the coordinates A/P: -2.6 mm and L: ±3.4 mm from Bregma, and D/V: -8.2 mm below the surface of the skull were used. For the NAc, the coordinates A/P: +1.4 mm and L: ±2.8 mm from Bregma, and D/V: -6.6 mm were used. After surgery, rats were housed individually and when they reached pre-surgical body weight, a saline test infusion was performed.

Diet intervention

Rats were placed on an *ad libitum* chow diet with tap water, or a free-choice high-fat high sugar-diet (fcHFHS) which allows *ad libitum* access to a dish of saturated beef tallow, a bottle of 30%w/v sucrose water, standard chow, and tap water (la Fleur et al., 2007). In the dose response for the NAc, only a fcHFHS group was included. Food intake was measured at least five times a week and all components were refreshed twice a week. Experimental infusions began after one week diet exposure.

Infusion parameters

Infusions were performed at the end of the light phase (between 16:30 and 17:30). All food components were removed from the cage before infusion. For the NPY1R-antagonist experiments in the LHA and NAc, 0, 0.3, 0.45 (only LHA), 1, 1.5 (only LHA) or 3 µg (only NAc) GR231118 in 0.2 µL PBS (sc-361194; Santa-Cruz Biotechnology Inc., Texas, USA; also known as 1229U91 or GW1229), or vehicle (0.2 µL 0.1 mol PBS) were infused bilaterally. For the NPY5R-antagonist experiment in the LHA, 0.5, 1, or 3 nmol L-152,804 (SML0891; Sigma-Aldrich, Missouri, USA) in 0.3 µL 4.45%, 8.9% or 26.67% DMSO respectively (D8418; Sigma-Aldrich) or vehicle (corresponding % DMSO in 0.3 µL 0.1 mol PBS) were infused bilaterally. In addition, 0.3 µL 50% DMSO was infused into three rats to determine the effects of a high DMSO percentage. Infusions were perfomed using an injector connected to a 10 µL Hamilton syringe placed in an infusion pump. Volumes were infused at a rate of 0.3 µL/min and infusion was confirmed by monitoring fluid movement in the tubing via a small air bubble. After infusion, the injector was left in place for 1 min to allow diffusion. Upon completion of all infusions, food was returned to the cages and weighed at 2, 4 and 22 hours after infusion.

Tissue collection

At the end of all infusions, rats were deeply anesthetized with an overdose pentobarbital, and epididymal fat pads were excised and weighed. Subsequently, rats were perfused transcardially with cold 0.9% saline followed by cold 3.8% formalin. Brains were removed and, after 24 hours postfixation, cryoprotected in 30% sucrose in PBS at 4 ˚C. Brains were then frozen on dry ice and stored at -80 ˚C. Subsequently, brains were sectioned coronally on a cryostat at 35 µm, and thionine staining was used to determin if cannulas were placed in the LHA or NAc.

Statistics and analyses

Only uni- and bilateral correct placements were included. Placement was determined according to the Paxinos rat brain atlas (Paxinos & Watson, 2007). For the NAc, correct placements were spaced from Bregma -2.28 till -0.96 mm and were contained in an area ventral to the lateral ventricles, medial to the anterior commissure, lateral to the Islands of Calleja (major island) and the vertical limb of the diagonal band, and dorsal to the medial forebrain bundle and ventral pallidum. For the LHA, correct placements were spaced from Bregma -2.28 till -3.72 mm and were contained in an area ventral to the zona incerta, medial of the internal capsula, and lateral to the dorsomedial and ventromedial hypothalamic nuclei.

Caloric intake was calculated for each food item and summed to determine total caloric intake. Dietary intervention measures were analyzed using a paired t-test. Epididymal fat pad weight is depicted per 100 gr body weight. The effects of the antagonists on food intake were not analyzed statistically due to low sample size in some of the groups. The effects of NPY on food intake are apparent in the first hours after infusion (Stanley & Thomas, 1993), therefore only data from the 2 hour timepoint is presented here, except for the DMSO conditions in the NPY5R-antagonist pilot. All data are presented as mean ± *SEM*.

Results

Effects of fcHFHS consumption

In pilot 1 (GR231118 in the NAc), only a fcHFHS-fed group was included. Data on caloric intake, body weight and fat mass is summarized in Table 1 for each of the diet groups. In the LHA pilots, both CHOW-fed and fcHFHS-fed groups were included. In pilot 2 (GR231118 in the LHA), CHOW- and fcHFHS-fed rats had similar initial body weight ($t_9 = 0.00$, $p > 0.05$). During the diet, fcHFHS-fed rats consumed a daily total caloric intake that was higher than that of CHOW-fed rats ($t_9 = 4.85$, $p < 0.001$). At the end of the diet, fcHFHS-fed rats had a higher body weight ($t_9 = 2.95$, $p = 0.02$), and more fat/100 gram body weight ($t_9 = 3.72$, $p = 0.005$) than CHOW-fed rats. fcHFHS-fed rats consumed an average of 38.2 ± 2.9 % of calories from chow, 32.6 ± 3.2 % from sugar water, and 36.3 ± 1.8 from fat. In pilot 2 (GR231118 in the LHA),

CHOW- and fcHFHS-fed rats had similar initial body weight (t_{10} = 0.34, p > 0.05). During the diet, fcHFHS-fed rats consumed a higher daily total caloric intake than CHOW-fed rats (t_{10} = 8.3, p < 0.0001). At the end of the diet, fcHFHS-fed rats had similar body weight (t_{10} = 1.2, p > 0.05), but more fat/100 gram body weight (t_{10} = 3.8, p = 0.004) than CHOW-fed rats. fcHFHS-fed rats consumed an average of 37.3 ± 2.8 % of calories from chow, 35.5 ± 4.1 from sugar water, and 23.4 ± 3.2 from fat.

Table 1. Summary of dietary intervention statistics.

	Pilot 1: NAc GR231118	Pilot 2: LHA GR231118		Pilot 3: LHA L-152,804	
	fcHFHS (N = 5)	CHOW	fcHFHS	CHOW	fcHFHS
Begin BW	302 ± 1.1	300 ± 4.0	300 ± 5.2	333.2 ± 2.4	334.3 ± 2.5
End BW	405 ± 6.5	359 ± 4.8*	379 ± 4.7*	398.2 ± 4.7	405.0 ± 4.7
Fat/100 gr BW	0.73 ± 0.05	0.50 ± 0.03	0.74 ± 0.05*	0.57 ± 0.03	0.80 ± 0.05*
TCI (kcal)	96.8 ± 12.2	65.9 ± 1.6	96.1 ± 5.5*	70.4 ± 3.7	105.1 ± 1.9*
Component					
Chow (%)	44.2 ± 1.9	-	38.2 ± 2.9	-	37.3 ± 2.8
Sugar (%)	48.4 ± 2.5	-	32.6 ± 3.2	-	35.5 ± 4.1
Fat (%)	8.3 ± 2.1	-	36.3 ± 1.8	-	23.4 ± 3.2

BW = body weight, Fat/100 gr BW = epididymal fat pad weight per 100 gr BW, TCI = mean daily total caloric intake, * P < 0.05 compared to the respective CHOW-fed group.

The effect of different doses NPY1R-antagonist GR231118 in the NAc on food intake

For the dose determination of GR231118 in the NAc, only a fcHFHS group was included. GR231118 did not pronouncedly decrease total caloric intake at any of the doses tested (data not shown). In addition, GR231118 did not pronouncedly affect intake of any of the dietary components. However, intake of each component was always slightly lower after infusion of GR23118 compared to saline infusion (see Figures 1A-D).

The effect of different doses NPY1R-antagonist GR231118 in the LHA on food intake

In the CHOW group, a dosis of 0.3 µg GR231118 did not affect intake compared to vehicle infusion, whereas a dosis of 0.45 µg GR231118 or higher, decreased intake 2 hours after infusion (Figure 2A).

In the fcHFHS group, a dosis of 0.3 µg GR231118 also did not affect total caloric intake intake compared to vehicle infusion, whereas a dosis of 0.45 µg GR231118 or higher, decreased total caloric intake 2 hours after infusion (Figure 2B). Intake of chow and fat was not decreased by 0.3 µg GR231118, but was decreased with a higher dose of 0.45 µg (Figure 2C, 2E). Intake of sugar water was decreased after 0.3 µg GR23118 (Figure 2D).

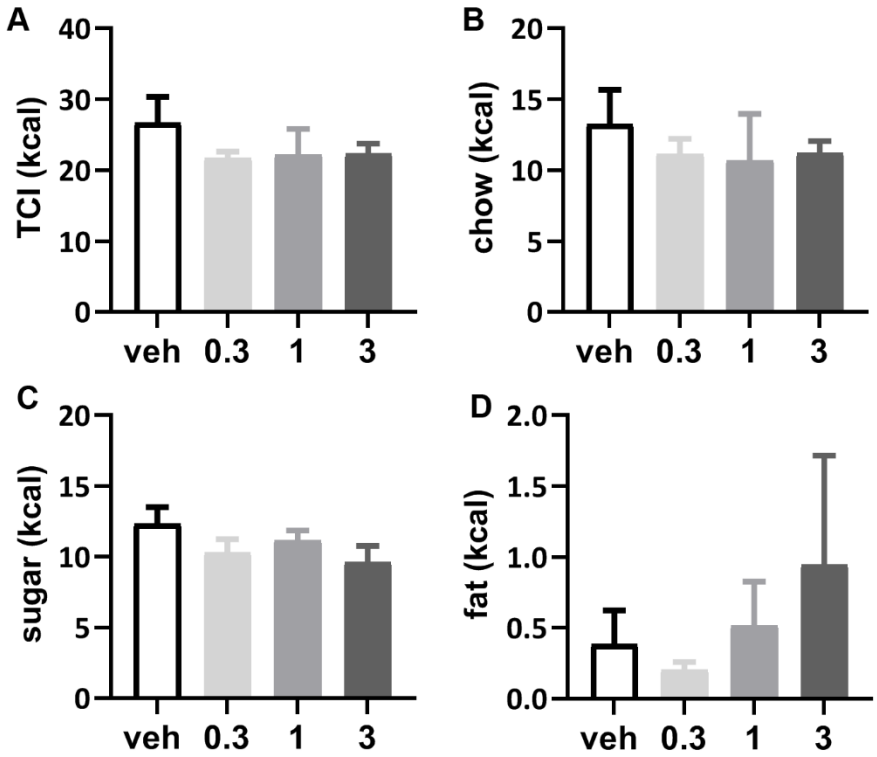

Figure 1. The effect of different doses NPY1R-antagonist GR231118 in the NAc on food intake. GR231118 was infused in the NAc of fcHFHS-fed rats at the end of the light period and food intake measured 2 hours later. **A)** Total caloric intake, **B)** caloric intake of chow, **C)** caloric intake of sucrose water, and **D)** caloric intake of fat. Note the difference in scale for 2D. Alle doses are in µg, TCI = total caloric intake, veh = vehicle, N = 4.

The effect of different doses NPY5R-antagonist L-152,804 in the LHA on food intake

In the CHOW group, a dosis of 0.5 nmol L-152,804 did not affect intake. Doses from 0.45 nmol and higher did seem to slightly affect intake. The largest dosis of 3 nmol L-152,804 decreased intake (Figure 3A).

In the fcHFHS group, total caloric intake was unaffected by any of the doses tested (Figure 3B). Intake of chow was also unaffected by any of the doses tested (Figure 3C), as well as intake of sucrose water (Figure 3E). Intake of fat seemed affected by different doses of L-152,804, although not in a systematic manner (Figure 4D).

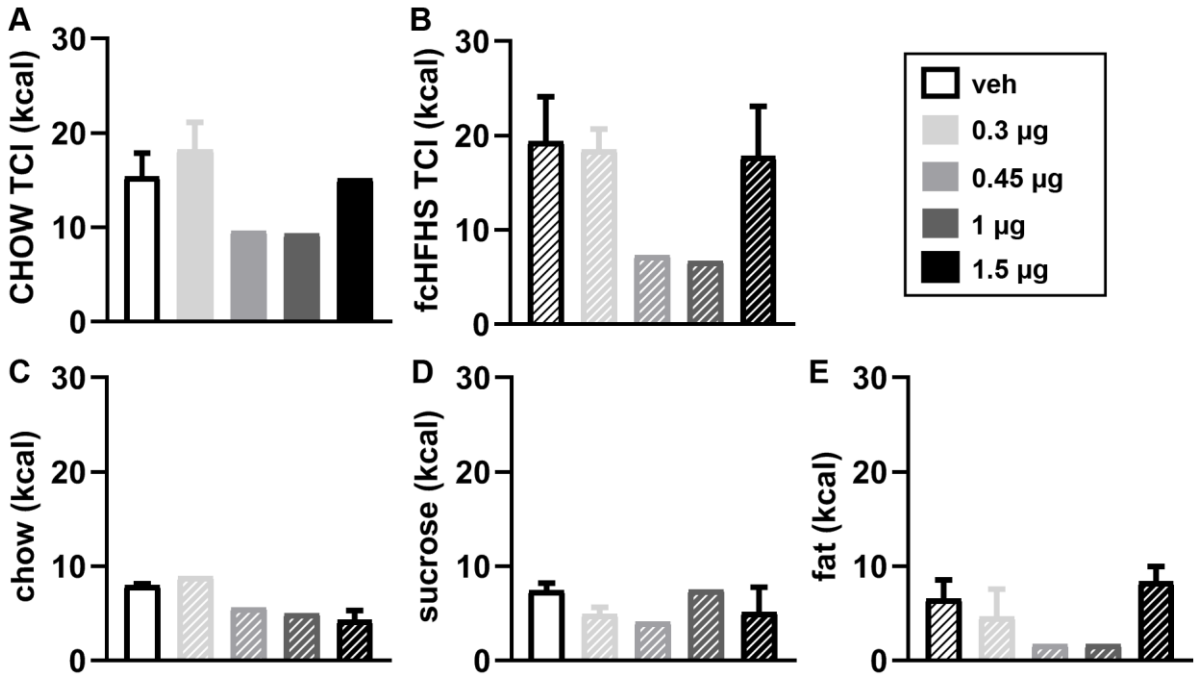

Figure 2. The effect of different doses NPY1R antagonist GR231118 in the LHA on food intake. GR231118 was infused in the LHA at the end of the light period and food intake measured 2 hours later. **A)** Total caloric intake (i.e. intake from chow) in CHOW-fed rats. In fcHFHS-fed rats (striped bars), **B)** total caloric intake, **C)** caloric intake of chow, **D)** caloric intake of sucrose water, and **E)** caloric intake of fat. TCI = total caloric intake, veh = vehicle. (N = 3, 3, 1, 1, 1 for the respective doses in the CHOW-group, and N = 3, 2, 1, 1, 2 for the respective doses in the fcHFHS-group).

The different doses of L-152,804 contained increasing concentrations of DMSO due to the chemical nature of L-152,804. DMSO can have detrimental effects on food intake behaviour, therefore DMSO percentage was also looked into. Tested with three rats, 50 % DMSO negatively afffected intake compared to a saline infusion (data not shown). Therefore, only lower doses of DMSO were used in subsequent infusions. Here, only caloric intake after the vehicle infusions (i.e. the saline and different DMSO infusions) is compared. In the CHOW group, 8.89 % and 26.67 % DMSO did not affect intake negatively as compared to saline infusion. However, at the 22 hour time point a negative effect on caloric intake was apparent compared to saline infusion (Figure 4A). In the fcHFHS group, no saline infusions were performed. In this group, 26.67 % DMSO decreased total caloric intake compared to 8.89 % DMSO at all time points (Figure 4B). For the chow and sugar water component, 26.67 % DMSO also decreased caloric intake compared to 8.89 % DMSO at all time points, whereas for the fat component, intake was higher after 26.67 % DMSO compared to 8.89 % DMSO (data not shown).

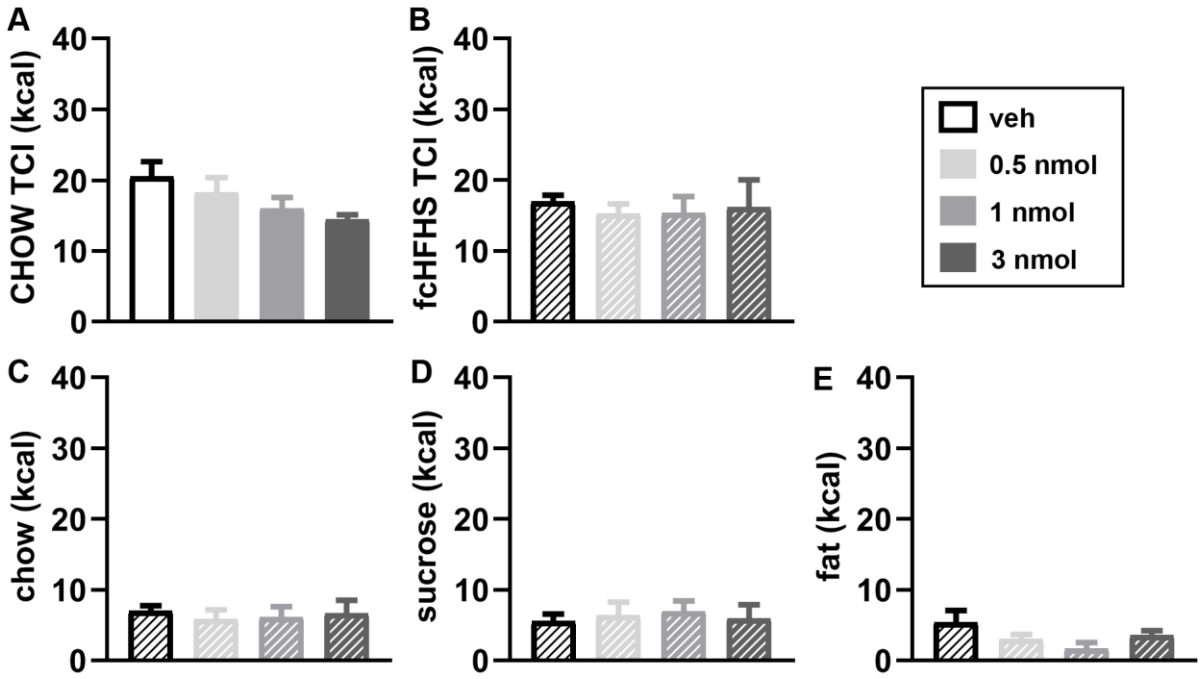

Figure 3. The effect of different doses NPY5R antagonist L-152,804 in the LHA on food intake. L-152,804 was infused in the LHA at the end of the light period and food intake measured 2 hours later. **A)** Total caloric intake (i.e. chow intake) in CHOW-fed rats. In fcHFHS-fed rats (striped bars), **B)** total caloric intake, **C)** caloric intake of chow, **D)** caloric intake of sucrose water, and **E)** caloric intake of fat. TCI = total caloric intake, veh = vehicle. (N = 6, 5, 6, 4 for the respective doses in the CHOW-group, and N = 6, 5, 6, 4 for the respective doses in the fcHFHS-group).

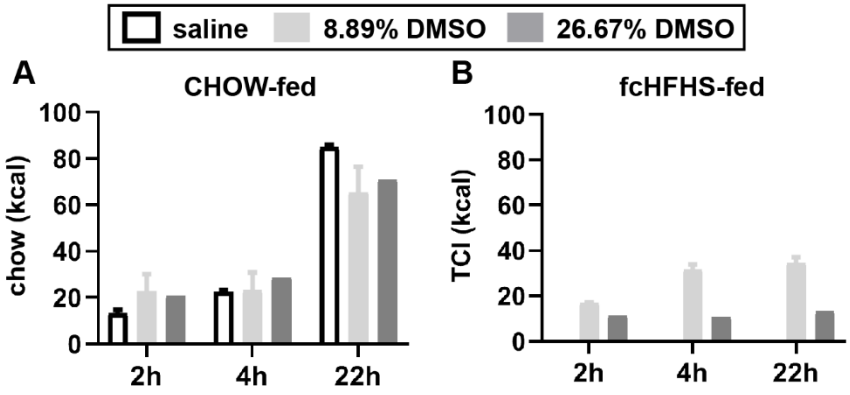

Figure 4. The effect of different doses of DMSO in the LHA on food intake in CHOW- and fcHFHS-fed rats. A) Caloric intake of CHOW-fed rats after different doses of DMSO, **B)** Total caloric intake of fcHFHS-fed rats after different doses of DMSO. For the CHOW-fed group: N = 6, 2 and 1 respectively for each dose. For the fcHFHS-fed group, N = 0, 3, and 1 respectively for each dose.

Discussion

Regarding NPY1R antagonism, intra-NAc GR231118 did not pronouncedly affect intake of any of the dietary components of fcHFHS-fed rats. However, intake after intra-NAc GR231118 infusion was always slightly lower than after vehicle infusion. We therefore concluded that the lowest dose of 0.3 µg was to be used in further experiments to determine whether the effects of intra-NAc NPY on intake were mediated via the NPY1R. Intra-LHA GR231118 did not affect intake of chow or fat at a dose of 0.3 µg in CHOW- or fcHFHS-fed rats. However, intake of all components was decreased after 0.45 µg infusion. Therefore, it was decided that the dose of 0.3 µg was to be used in further experiments to determine whether the effect of intra-LHA NPY was mediated via the NPY1R.

It is important to note that in the LHA, NPY1R-antagonist infusion could affect caloric intake in both diet groups at the start of the dark period when LHA NPY levels might be high and rats are preparing to feed ([Akabayashi et al., 1994; McKibbin et al., 1991]; though see [Jhanwar-Uniyal et al., 1990]). This might indicate that NPY is released in the LHA endogenously at this time point to regulate feeding behavior physiologically as *in vitro* assays have not shown constitutive activity for the NPY1R (E. M. Parker et al., 1998), which might have been another explanation. On the other hand, NPY1R-antagonism in the NAc did not clearly affect intake when infused on its own. Though only a small sample size, this might indicate that endogenous release is not as important in regulating feeding in the NAc at the start of the dark period, and again provides evidence against constitutive activity of the NPY1R. Future studies could explore this in more detail.

Regarding NPY5R antagonism, intra-LHA L-152,804 decreased intake when infused at a high dose in CHOW-fed rats, whereas none of the L-152,804 doses decreased intake of the dietary components of fcHFHS-fed rats. As the NPY5R-antagonist was dissolved in DMSO, this was also taken into account when deciding with which dose to proceed with. As the highest L-152,804 dose was dissolved in 26.67 % DMSO, this might have affected intake. This was not apparent at the 2-hour time point, but was apparent at the 22-hour time point. In addition, the low solubility of L-152,804 limited the dose range to the nanomolar range. The dose to be used in further experiments was therefore a compromise between DMSO percentage and the highest dose that could be dissolved; 1 nmol.

Technical considerations

These technical considerations have been reported before in chapter VI. The NPY1R-antagonist GR231118 is a highly potent competitive NPY1R-antagonist, but also a NPY4R-agonist (E. M. Parker et al., 1998; Schober et al., 1998). As intracerebral NPY4R activation leads to *increased* intake (Campbell et al., 2003), and NPY4R has a low affinity to NPY (Gerald

et al., 1996), GR231118 seems valid to use to determine whether the effects of NPY-induced intake are mediated by the NPY1R.

The NPY5R-antagonist L-152,804 is highly potent and highly selective for the NPY5R, which was also confirmed by lack of effect in NPY5R KO mice (Ishihara et al., 2006; Kanatani et al., 2000). However, the chemical nature of L-152,804 leads to low solubility and requires dissolving in DMSO, which, as mentioned before, could be detrimental to feeding behavior. Together, this limited the range of the doses that could be tested. Unfortunately, other NPY5R-antagonists have not been characterized as extensively and have not been tested using intracerebral infusion. Therefore, the dose that was chosen for future studies might not be optimal and it is recommended to assess the effects of DMSO by monitoring intake of kaolin after DMSO infusion. Though the effects of DMSO were only apparent at a very high percentage (50%) and at later time points, when it might not interfere with the direct effect of NPY infusion, kaolin intake is an indication for nausea in animals that cannot vomit (Goineau & Castagne, 2016). In addition, it is recommended to include a saline infusion in the fcHFHS group for a more accurate comparison of the effects of DMSO on intake.

Conclusions

1) The Y1-antagonist GR231118 does not alter caloric intake in fcHFHS-fed rats when infused at a dose of 0.3 µg in the NAc at the beginning of the dark period to block endogenous NPY.
2) The Y1-antagonist GR231118 does not alter caloric intake in fcHFHS- or CHOW-fed rats when infused at a dose of 0.3 µg in the LHA at the beginning of the dark period to block endogenous NPY.
3) The Y5-antagonist L-152,804 does not alter caloric intake in fcHFHS- or CHOW-fed rats when infused at a dose of 1 nmol in the LHA at the beginning of the dark period to block endogenous NPY.

Acknowledgements

I would like to thank Leslie Eggels for her indispensable contribution with the procedures for the animal experiments, and Anneke Vuuregge and Tess Kool for their assistance with the procedures of the animal experiments. I would also like to thank Unga Unmehopa, Tess Kool, and Tessa Roelofs for the laboratory work and determination of cannula placements.

Appendix III. PhD Portfolio

	Year	Workload (ECTS)
1. PhD Training		
Courses		
- Workshops and courses related to education and educational design	2018 –	4+
- Advanced qPCR, AMC-UvA	2017	0.7
- Practical Biostatistics, OOA/AMC-UvA	2017	1.1
- Language course French; beginner and advanced, NHA	2017	4+
- Basic course Microscopy, AMC-UvA	2016	1.6
- Radiation protection (art. 5B), AMC-UvA	2014	1.7
- Crash Course, AMC-UvA	2014	0.4
- Laboratory animal science (art. 9)	2014	3.9
Seminars, workshops, and master classes		
- UvA education day	2019	0.5
- UvA education day	2018	0.5
- Workshop didactical skills, AMC-UvA	2017	0.4
- Workshop systematic reviews, Syrcle	2015	0.4
- Workshop Grants, AMC-UvA	2015	0.1
- Workshop Endnote, AMC-UvA	2014	0.1
- Nutribrain Summer school, Bordeaux	2014	4
- Weekly research meeting Endocrinology	2014 – 16	4
Oral presentations		
- Science Exchange Day, Amsterdam, NL	2019	0.5
- Amsterdam Gastroenterology and Metabolism (AG&M), Garderen, NL	2018	0.5
- Society for the Study of Ingestive Behavior (SSIB), Toronto, Canada	2017	0.5
- Amsterdam Gastroenterology and Metabolism (AG&M), Garderen, NL	2017	0.5
- Amsterdam Gastroenterology and Metabolism (AG&M), Garderen, NL	2016	0.5
- Nutribrain Summer school, Bordeaux, France	2014	0.5
Poster presentations		
- Society for the Study of Ingestive Behavior (SSIB), Porto, Portugal	2016	0.5
- Dutch Neuroscience meeting, Lunteren, NL	2017	0.5
- European Molecular Biology Organization (EMBO), Cascaís, Portugal	2016	0.5
- Society for the Study of Ingestive Behavior, Denver, USA	2015	0.5
- Endo-Neuro-Psycho meeting (former DN), Lunteren, NL	2015	0.5
- Nutribrain summerschool, Bordeaux, France	2014	0.5
- Endo-Neuro-Psycho meeting, Lunteren, NL	2014	0.5
(Inter)national conferences		
- Science Exchange Day, Amsterdam, the Netherlands	2019	0.6
- Amsterdam Gastroenterology and Metabolism (AG&M), Garderen, NL	2018	1
- Society for the Study of Ingestive Behavior (SSIB), Toronto, Canada	2017	1
- Amsterdam Gastroenterology and Metabolism (AG&M), Garderen, NL	2017	1
- Dutch Neuroscience meeting (DN), Lunteren, NL	2017	1
- The Netherlands Association for the Study of Obesity (NASO), Utrecht, NL	2017	0.5
- Amsterdam Gastroenterology and Metabolism (AG&M), Garderen, NL	2016	1

- Society for the Study of Ingestive Behavior (SSIB), Porto, Portugal	2016	1.25
- European Molecular Biology Organization (EMBO), Cascaís, Portugal	2016	1.25
- Amsterdam Neuroscience, Amsterdam, NL	2016	0.5
- Society for the Study of Ingestive Behavior (SSIB), Denver, USA	2015	1.25
- Endo-Neuro-Psycho meeting (former DN), Lunteren, NL	2015	1
- ACM-MDL (former AG&M), Lunteren, NL	2015	1
- Endo-Neuro-Psycho meeting (former DN), Lunteren, NL	2014	1
- The Netherlands Association for the Study of Obesity, Oosterbeek, NL	2014	0.5
Organizational participation and other		
- Research Institute Representative, Science Exchange Day, NL	2019	0.4
- Steering committee of PhD retreat of the Amsterdam Gastroenterology and Metabolism (AG&M)	2015 – 18	4+
- Secretary and program director of the New Investigator Advisory Board of the Society for the study of ingestive behavior (SSIB)	2015 – 17	4+
- Organizer of research group weekly journal club	2015 – 16	1
- PhD competency model discussion group	2015	0.5
- Organizer of research group Symposium and social group trips	2014 – 18	2
2. Teaching		
- Basis Kwalificatie Onderwijs University of Amsterdam	2019	4+
- Teaching and mentoring academical skills (BSc Psychobiology)	2017 –	4+
- Teaching and supervising thesis writing (BSc Psychobiology)	2017 –	4+
- Volunteer IMC Weekendschool for primary and secondary education	2017	0.8
- Lecture animal experimentation for Master course Endocrinology	2015	0.5
- Supervision of interns at MLO, HLA, and university level (BSc and MSc)	2015 – 19	4+
3. Parameters of esteem		
Grants and prizes		
Poster award Dutch neuroscience (sponsored by the Neuroscience Campus Amsterdam, the Netherlands)	2016	
AMC PhD Scholarship (AMC, the Netherlands)	2014	

NL = the Netherlands, USA = United States of America

Publications

Gumbs, M. C. R., Eggels, L., Vuuregge, A. H., Unmehopa, U. A., Mul, J. D., and la Fleur, S. E. (*Submitted*). Dietary choice and composition modulate the orexigenic effects of Neuropeptide Y in the lateral hypothalamus of the male Wistar rat.

Gumbs, M. C. R., Eggels, L., Kool, T., Unmehopa, U. A., van den Heuvel, J. K., Lamuadni, K., Mul, J. D., and la Fleur, S. E. (*accepted*). Neuropeptide Y signaling in the lateral hypothalamus modulates diet component selection and is dysregulated in a model of diet-induced obesity. *Neuroscience*

Gumbs, M. C. R., Vuuregge, A. H., Eggels, L., Unmehopa, U. A., Lamuadni, K., Mul, J. D., and la Fleur, S. E. (2019). Afferent neuropeptide Y projections to the ventral tegmental area in normal-weight male Wistar rats. *Journal of Comparative Neurology*, 527(16):2659-2674, doi: 10.1002/cne.24698

Slomp, M., Belegri, E., Blancas-Velazquez, A. S., Diepenbroek, C., Eggels, L., **Gumbs, M. C. R.,** Joshi, A., Koekkoek, L. L., Lamuadni, K., Ugur, M., Unmehopa, U., A., la Fleur, S. E., and Mul, J. D. (2019). Stressing the importance of choice – validity of a preclinical free-choice high-caloric diet paradigm to model behavioral, physiological, and molecular adaptations during human diet-induced obesity and metabolic dysfunction. *Journal of Neuroendocrinology*,31(5):e12718, doi: 10.1111/jne.12718

Gumbs, M. C. R., van den Heuvel, J. K., and la Fleur, S. E. (2016). The effect of obesogenic diets on brain Neuropeptide Y. *Physiology of Behavior, 162,* 161-173, doi: 10.1016/j.physbeh.2016.04.049

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Krugers, H. J., Oomen, C. A., **Gumbs, M. C. R.,** Li, M., Velzing, E. H., Joëls, M., and Lucassen, P. J. (2012). Maternal deprivation and dendritic complexity in the basolateral amygdala. *Neuropharmacology, 62(1),* 534-537, doi: 10.1016/j.neuropharm.2011.09.022

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Acknowledgements – Dankwoord

Toen ik begon aan het promotietraject had ik geen idee over de grootte van de taak die ik op me had genomen. Ik was vooral erg enthousiast over het onderwerp van mijn onderzoek; Neuropeptide Y. Gedurende het traject ben ik erachter gekomen hoe belangrijk externe factoren kunnen zijn bij het behalen van je doelen. Een positieve factor was de steun van de mensen om mij heen. Ik heb altijd geprobeerd iedereen te bedanken op het moment zelf, maar ik maak graag gebruik van deze kans om mijn waardering op schrift te stellen.

Geachte promotoren, **Prof. dr. Susanne la Fleur** en **Prof. Dr. Jan Booij**, en copromotor, **dr. Joram Mul**, ik waardeer het enorm dat ik de afgelopen jaren bij jullie mijn onderzoek heb kunnen uitvoeren.

Beste **Susanne**, jij bent vanaf het begin betrokken geweest vanaf mijn stage in 2012, waarin we hadden besloten een AMC PhD beurs aan te vragen. Ik kon toen kiezen tussen twee plaatsen en ik was heel blij dat we de beurs hadden gekregen en dat ik bij jou een betrokken begeleider gevonden had. Kenmerkend aan jouw begeleiding is de zelfstandigheid van de student en de steun voor de zelfontwikkeling. Je hebt me de ruimte gegeven en volop kansen geboden om mezelf te ontwikkelen zoals de vele congresbezoeken en de mogelijkheid om tijdens mijn promotie parttime te werken zodat ik me kon ontwikkelen in de didactiek als docent op de UvA. Heel erg bedankt hiervoor!

Beste **Jan**, ik heb het erg gewaardeerd om met jou de data en de voortgang te bespreken. Onze besprekingen heb ik altijd als gezellig ervaren waarbij er een frisse blik over de data heen ging vanuit een ander perspectief. Ook dank voor de snelle en kritische blik op mijn manuscripten.

Beste **Joram**, vlak voordat ik ook als docent aan de slag ging, werd jij mijn copromotor. Ik heb jouw positieve houding erg gewaardeerd. Bedankt voor het geduld met het omzetten van mijn liefde voor Excel grafiekjes in elegantere Graphpad grafieken, en het introduceren van het programma Illustrator. Ook dank voor je gefocuste aandacht bij het reviseren van mijn teksten en de esthetiek van onze publicaties. Ik denk dat dit belangrijk is geweest voor de snelle acceptatie en publicatie van onze manuscripten.

Geachte leden van de promotiecommissie, **Prof. dr. Swaab, Prof. dr. Kalsbeek, dr. Yi, dr. Meye, Prof. dr. Adan, dr. ing. Olivier** en **Prof. dr. Lucassen**, dank voor uw bereidheid zitting te nemen in de promotiecommissie en het beoordelen van mijn manuscript.

Dank ook aan het **diagnostische lab van de Endocrinologie** voor de gezelligheid, collegialiteit en vele (lunch) gesprekken over van alles en nog wat, in het bijzonder met **Schreyas, Cecilia, Fred, David, Ivy, Yvonne, Dewi, Henk** en **Ephraim**. **Annemiek**, bedankt voor je interesse in mijn voortgang naast al je werkzaamheden. **Angeline, Birgit** en **Anna**, bedankt ook voor alle secretariële hulp. **Señora Li**, señora su sonrisa semper ta hasi mi contentu anto ta zorg pa un felis día di traha. Masha danki!

De Research afdelingen van het Amsterdam UMC en NIN hebben de afgelopen jaren veel collega's en (oud)collega's opgeleverd. Het is onmogelijk om iedereen te bedanken die een bijdrage geleverd heeft. Aan alle leden van de Research daarom dank voor de collegialiteit en (wetenschappelijke) input bij meetings en in de wandelgangen. Het was erg fijn zulke leuke collega's te hebben gehad!

Lieve **Leslie en Unga**, bikkele analisten, ik hoop dat ik jullie tijdens het werk vaak genoeg heb gezegd hoe fijn ik jullie expertise, professionaliteit, gezelligheid en nuchtere steun heb gevonden. Ik heb onze samenwerking enorm gewaardeerd en ben erg blij dat we de laatste fase ook samen doen. Zonder jullie was deze thesis niet 11 hoofdstukken geworden en was ik nu nog bezig. Ontzettend bedankt!

Charlene, de afgelopen jaren heb ik het leerzaam gevonden met jou te sparren over allerlei zaken. Dank voor je betrokkenheid, gezelligheid en integriteit. **Laura, Margo** en **Stan,** ik vond het leuk om met jullie te lunchen en te zien hoe de 'nieuwe garde' projecten aanpakt. Succes nog even! Dank ook aan de studenten die bij mijn projecten betrokken zijn geweest, **Karlijn, Christel** en **Bernadine.** In het bijzonder **Khalid** en **Tess,** die inmiddels collega's zijn geworden, en **Anneke** natuurlijk; jullie drieën hebben zo vlot gewerkt en waren zo snel zelfstandig dat jullie werk inmiddels in een aantal publicaties staat. Dank voor jullie inzet bij de projecten! **Clarissa**, I enjoyed meeting you and discussing science with you.

Dr. Mireille, hoofd van Serlie groep, bij de gezamenlijke besprekingen op maandag voeg jij altijd een vrolijk doch kritische noot toe**. Katy**, dank voor je uitleg over jouw D2 projecten en vrolijke humor op de afdeling. Heel leuk dat je met **Sabrina** en **Jamie** het End-of-the-Year Symposium voortzet.

Ewout, in tijden van nood gaf jij de mogelijkheid een kleine proef op te zetten wat heeft geleid tot twee hoofdstukken in mijn thesis en ook door anderen wordt gebruikt. Super bedankt voor al je hulp! **Paul**, jouw werkethos en positieve levensfilosofie zijn een bron van inspiratie geweest. **Fernando**, I should write this in French because you taught me well, or in Dutch because you learned so well. Thank you for your motivation and friendliness! **Martin**, jouw humor, en **Nikita**, jouw vrolijkheid waren altijd welkome afleidingen.

Cora, met jouw kennis en ervaring hebben we onze eerste proef in het IWO-lab vlot gedaan. Bedankt voor al je hulp, expertise en gezelligheid!

Rawien, bedankt voor alle hulp met Niepke antilichaam en de gezellige gesprekken.

Daarnaast natuurlijk ook dank aan vele (oud-)collega's, **Anita, Anil, Anne, Anneloes, Aurea, Chun-Xia, Daniela, Dries, Emmely, Eric, Evita, Esmay, Flavia, Hannah, Irina, Joëlle, José, Kasper, Kevin, Mariëtte, Merel, Mieke, Marianne, Müzzeyen, Murat, Olga, Remi, Rianne, Satish, Tessel, Wayne, Yan, Zhi**. Hoewel het soms een tijd geleden is, ben ik jullie niet vergeten. Heel erg bedankt voor alle gezelligheid en wetenschappelijke inbreng. **José**, het begon allemaal met een stage bij jou. Bedankt voor de introductie met NPY. **G2-kamergenoten**, dank voor de leuke tijden! Ik heb zo veel van jullie geleerd!

Uiteraard ook dank aan **Joop** en **Joris** voor alle hulp met de verschillende microscopen! Ook dank aan **Rainier, Jacques, Natasja** en de **medewerkers van het ARIA** voor de verzorging van onze ratten.

Beste **collega's aan de UvA**, bedankt voor alle collegialiteit, vriendelijkheid en (didactische) kennisoverdracht de afgelopen jaren.

Heel veel dank ook aan mijn familie en vrienden voor hun interesse, steun en gezelligheid.

Sophie A, Niguel, Erik, Cynthia, Psychobioos: Jolien, Steffie en **Anouk,** en daarnaast ook **Sophie B**, met jullie vergeet ik de tijd. Jullie helpen me eraan herinneren hoe veel leuke dingen er zijn naast werk! **Kathy**, tof dat we elkaar als collega-vrienden hebben ontmoet!

Lieve schoonfamilie, **Geert** en **Désirée**, bedankt voor jullie hartelijke interesse de afgelopen jaren. Natuurlijk ook bedankt voor alle chocolade! **Iris**, ik vind het erg gezellig om jou en Didier op te zoeken op jullie exotische adressen.

Lieve **mam** en **pap**, heel erg bedankt voor alle ervaringen en liefde die jullie me hebben meegegeven. **Mam**, bedankt dat je me altijd uitdaagt het positieve en holistische van een situatie in te zien. Ik vind jouw energieke en ondernemende geest en jouw oplossings-gerichtheid uitzonderlijk. **Pap**, ik vind het heel jammer dat je mijn promotie niet hebt kunnen meemaken. Je bent altijd in mijn gedachten en een mentale kracht om door te zetten en het goede te doen voor de mensen om mij heen. Lieve **oma**, het was altijd gezellig bij je op bezoek en er even uit te zijn. Ik had je graag mijn boekje laten zien.

Didier en Riëlette, we begonnen als een 'drie-eenheid' en zijn nu allerlei kanten op gestuiterd. Het is heerlijk om met z'n drieën samen te zijn en te keten. **Didier**, jouw rust, avontuurlijkheid en nuchterheid bieden altijd nieuwe perspectieven in allerlei situaties. **Riëlette**, onze gesprekken over van alles en nog wat en je steun, niet alleen tijdens de promotie maar altijd, waardeer ik enorm. Je kan tegelijkertijd lief, attent en principieel zijn. Samen met jouw objectieve kijk heb je me daardoor vaak nieuwe opties laten zien en push je me om tot actie over te gaan als ik in gedachten blijf ronddwalen. Ik ben ontzettend blij dat je, samen met Leslie en Unga, één van mijn paranimfen wilt zijn.

Lieve **Wybe**, woorden schieten te kort als ik wil opschrijven wat jouw aanwezigheid voor me betekent. Bedankt voor al je steun en je verrassende humor die me altijd aan het lachen maakt. Ik vind het heerlijk om met je samen te zijn en een huishouden te voeren. Jouw kwaliteiten blijven me verrassen en motiveren mij. Met jou is alles leuker en is de zomer voor altijd.

About the author

Myrtille Cannelle Rojani Gumbs (22nd May, 1989) was born in Philipsburg, Saint Maarten, the Netherlands Antilles, to Dr. R.R. Gumbs and J.E. Pater. After attending the Oranje School until grade 4, she moved to Amsterdam, the Netherlands, and finished primary school at the 16e Montessori school Amsterdam. She did a double program in science at the Scholengemeenschap Reigersbos and passed with distinction. Being very interested in the brain and how it works, Myrtille obtained a Bachelor's degree in Psychobiology (including an honors program and passing with distinction) and a Master's degree in *Psychopathology, pathophysiology and pharmacology* at the University of Amsterdam. She performed an internship in the Lucassen group at the Swammerdam Institute for Life Sciences (subject: neuroanatomy of the Basolateral Amygdala after maternal deprivation), and an extended internship in the la Fleur group at the Academic Medical Centre (AMC) Amsterdam (various projects including her first introduction to Neuropeptide Y and food intake behavior). She extended her Master's program with an internship in the Borgland lab at the University of British Columbia and the University of Calgary in Canada (subject: electrophysiological effects of Neuropeptide Y on Ventral Tegmental Area dopamine neurons using whole cell patch clamping). During her stay abroad, she was awarded an AMC PhD scholarship to work in the la Fleur group on the role of Neuropeptide Y in feeding behavior. During her PhD her studies focused on behavior, gene expression, pharmacology and neuroanatomy. Having experienced much pleasure in supervising interns, Myrtille started teaching students of the Bachelor Psychobiology part-time at the University of Amsterdam during her fourth PhD year. She has finished writing her thesis and will keep on studying and teaching matters related to the brain in the near future.