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Peer-reviewed author version

Vloeberghs, Ellen; Van Dam, Debby; Franck, Frieda; Staufenbiel, Matthias; SERROYEN, Jan; MOLENBERGHS, Geert & De Deyn, Peter Paul (2008) Altered ingestive behavior, weight changes, and intact olfactory sense in an APP overexpression model. In: BEHAVIORAL NEUROSCIENCE, 122(3). p. 491-497.

DOI: 10.1037/0735-7044.122.3.491
Handle: http://hdl.handle.net/1942/8328

ALTERED INGESTIVE BEHAVIOR, WEIGHT CHANGES AND INTACT OLFACTORY SENSE IN AN APP OVEREXPRESSION MODEL

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Running title: Eating & drinking behavior in the APP23 model

Manuscript: contains 23 pages, 1 figure, 1 table

Word count: whole manuscript (3377, N/I references, tables and graphs), abstract (223), introduction (500), discussion (1023)

Date of submission: April 2007

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Abstract

Transgenic APP23 mice which overexpress the human amyloid precursor protein encoding the Swedish double mutation were generated to model Alzheimer's disease. The APP23 model develops pathological features and learning and memory deficits analogous to the dementing patients. We have reported these transgenic mice to exhibit several behavioral disturbances indicating moreover the presence of neuropsychiatric symptoms of dementia. With the aim of verifying whether the model also develops other behavioral problems, the present study investigated ingestive behavior in APP23 males of 3, 6 and 12 months of age. In addition body weights of a naive group of males were longitudinally monitored starting at weaning. Moreover, olfactory acuity was monitored in mice of different age groups. While olfactory functioning of the transgenic mice appeared intact, APP23 mice drank more and took a higher number of food pellets compared to wild-type littermates during a 1-week registration period. Surprisingly, from the age of 4.5 weeks onwards, APP23 males weighed significantly less than their control littermates whereas this difference became even more prominent with increasing age. Our results support the hypothesis of the existence of a hypermetabolic state in Alzheimer's disease. This is the first report, evidencing the presence of changes in both eating and drinking behavior in a single transgenic Alzheimer mouse model. APP23 mice become an even more promising and valuable animal model for dementia-related research.

Keywords: Alzheimer's disease, transgenic mouse model, Skinner box, ingestive behavior, eating, drinking, growth curve, olfaction

Introduction

Alzheimer's disease (AD) and other dementias are defined by cognitive and non-cognitive symptomatology. These neuropsychological characteristics are referred to as BPSD. Besides these behavioral and psychological signs and symptoms of dementia described by Reisberg *et al.* (1987), dementing patients frequently develop changes in ingestive behavior. Mirakhur *et al.* (2004) found appetite or eating disturbances in 63.7% of probable AD patients. Studies in dementing populations have described 11-13% to develop a preference for sweets; 19-24% shows increased consumption, while 22-66% tends to decrease food intake and 3-17% eats inedible substances (Cullen *et al.*, 1997; Hope *et al.*, 1997; Keene *et al.*, 1998; Morris *et al.*, 1989). Abnormal eating behaviors may contribute to weight fluctuations, however it is not clear whether weight loss is a core symptom or secondary manifestation. Weight loss also occurs in early disease stages and is the commonest alteration, although some patients gain weight (Mazzali *et al.*, 2002; Morris *et al.*, 1989; White *et al.*, 1994). White *et al.* (1996) showed that nearly twice as many subjects with AD experienced a weight loss of ≥5% compared with controls. Various hypotheses have been postulated with regard to weight loss: failure of body weight regulation, elevated resting energy expenditure, hypermetabolism or increased energy expenditure (e.g. resulting from wandering activities), and self-feeding difficulties (Keller *et al.*, 2003; Rheaume et al., 1987). Feeding difficulties might originate for instance from self-neglect, forgetting or refusal to eat, or changes in taste and olfaction. The latter is a feature occurring in 23% of AD patients, versus 6.7% of healthy elderly people (Olichney *et al.*, 2005). However, all of the above factors may contribute and the aetiology of weight loss in AD does indeed appear multifactorial (Grundman *et al.*, 1996).

In animal models of dementia, weight changes and ingestive behavior have only scarcely been investigated. Weight loss, accompanied by active rejection of food and water lasting 2-4 days, was previously found in rats with lesions of the nucleus basalis (Whishaw *et al.*, 1985).

Miyamoto (1994) reported higher water intake in the SAMP8 compared with the SAMR1 control. A recent study of Pugh et al. (2007) reported increased feeding behavior and reduced body weight in an APP/PS1 model.

The APP23 model carries the Swedish mutation, known to cause early-onset AD, and was generated to model dementia (Sturchler-Pierrat *et al.*, 1997). The transgenic mice do not only develop cognitive problems with age, our group has recently reported the development of several BPSD, among which activity disturbances and increased levels of aggressiveness (Van Dam *et al.*, 2003; Vloeberghs *et al.*, 2004; Vloeberghs *et al.*, 2006a; for review: Van Dam *et al.*, 2005). The present study aimed to investigate whether this valuable mouse model develops eating and drinking disturbances as well. Since the pathological hallmarks of AD are present in brain regions involved in processing olfactory input, and olfactory dysfunction might be a reason for weight loss, we additionally investigated olfactory functioning in the APP23 model. This study moreover provides an overview of body weight evolution in male APP23 mice.

Materials and methods

Transgenic mouse model

Transgenic APP23 mice were genetically engineered in a hybrid C57BL/6 x DBA2 background by Sturchler-Pierrat *et al.* (1997). The neuron-specific murine Thy-1.2 promoter drives human amyloid precursor protein (APP) 751 cDNA encoding the Swedish double mutation (K670N/M671L), which is known to cause familial AD. The generated mice were backcrossed to the C57BL/6J strain for at least 20 generations to provide an isogenic line. Genotypes (i.e. the presence or absence of the transgenic construct) were identified by polymerase chain reaction, as previously described (Vloeberghs *et al.*, 2006b).

Male heterozygous APP23 mice and wild-type (WT) control littermates were bred within our facilities by crossing APP23 males with control inbred C57BL/6J females. They were group housed in standard mouse cages (38.2 x 22 x 15 cm; length x width x height) with sawdust as bedding material and under conventional laboratory conditions; constant room temperature (22 ± 2 °C), humidity level (55 ± 5 %), a 12-h light:12-h dark cycle (lights on at 8 AM) and food (Carfil, Oud-Turnhout, Belgium) and water available *ad libitum*.

All experiments were approved by the Animal Ethics Committee of the University of Antwerp and performed in accordance with the European Communities Council Directive (86/609/EEC).

Eating and drinking behavior

Eating and drinking behavior were simultaneously recorded by employing Skinner boxes placed inside ventilated isolation compartments. Each mouse cubicle (Habitest - Coulbourn Instruments, Allentown, USA) was equipped with a pellet feeder to provide 20 mg dustless precision pellets of the rodent grain-based formula (BioServ, Frenchtown, USA) and a water bottle with optical lickometer delivering tap water. Photocell sensors were used to detect

pellet removal, i.e. the number of pellets taken, and the number of licks at the drinking tube. Registration periods typically started Wednesday at 10 AM and ended exactly 167 hours later on Wednesday at 9 AM. During this 1-week recording period, the 12-h light:12-h dark cycle was continued in the same way as in the facility where mice were previously housed (i.e. lights off at 8 PM). Eating and drinking behavior were registered in different naive groups of male transgenic APP23 mice and their wild-type littermates at 3 (WT n = 14; APP23 n = 13), 6 (WT n = 13; APP23 n = 13) and 12 (WT n = 17; APP23 n = 15) months of age. For quantitative analysis of food intake, meals were defined as minimum five pellets with a minimum inter-meal interval of 10 minutes. Individual licks were grouped into drinking sessions of minimum 20 licks, with two drinking sessions also separated by minimum 10-minute intervals.

Growth curves

Naive mice (WT n = 36; APP23 n = 24) were weighed twice a week starting at weaning (i.e. at the age of 4 weeks) until the age of 12 weeks. Subsequently their body weight was followed up monthly (Kern balance, Eupen, Belgium).

Investigation of the olfactory system

Olfaction was investigated using the food tunnel test, a new paradigm we developed to evaluate olfactory sense. Animals were kept on a reversed 12-h light:12-h dark cycle (lights on at 8 PM) and were food deprived for 19 h – 22 h prior to testing, with water available *ad libitum*. The new apparatus consists of a central box (15 x 10 x 15 cm; length x width x height) from which two 20-cm tunnels lead to the tunnel ends. These tunnel ends are separated from the rest of the apparatus by a low wall, which in the target arm hides several food pellets from view, but where a mouse can easily climb over. The apparatus is non-

transparent and the top is open, so all mouse movements can be traced by camera and registered with the Ethovision tracking system (Noldus, Netherlands). The test is computer monitored until the food pellets are found or up to a maximum of 5 minutes. Parameters measured were the latency to the first arm entries, number of entries and the percentage of time spent in the central area, the non-target and target arm. Olfactory acuity was evaluated in mice of four age groups; 6-8 weeks (WT n = 11; APP23 n = 9), 3 (WT n = 23; APP23 n = 24), 6 (WT n = 30; APP23 n = 17) and 12 (WT n = 22; APP23 n = 17) months.

Statistical analysis

Eating and drinking behavior were analysed by means of two-way (repeated) measures analyses of variance (2-way (RM) ANOVA), considering genotype, age or day/night as possible sources of variation. Significance of differences between means of body weight was assessed using 2-way RM ANOVA with Tukey HSD as post hoc comparison procedure. All statistical analyses were performed using SigmaStat software (SPSS Science, Erkrath, Germany) with the level of probability set at 95 %.

Results

We found heterozygous APP23 mice to take a higher number of food pellets than wild-type mice. They took on average 2135 ± 84 pellets during a period of 1 week versus 1861 ± 81 pellets taken by the control group (2-way ANOVA; $F_{1,79} = 5.532$; $P = 0.021$). In comparison with their wild-type littermates, APP23 mice performed significantly more licking responses as well, i.e. 35084 ± 1741 versus 29097 ± 1687 ($F_{1,79} = 6.100$; $P = 0.016$). We were not able to demonstrate an age-dependent effect on eating or drinking behavior (2-way ANOVA; $F_{2,79} = 1.449$; $P = 0.241$, $F_{2,79} = 2.785$; $P = 0.068$, respectively). Neither were there significant interactions between genotype and age (eating; $F_{2,79} = 0.0985$; $P = 0.906$, drinking; $F_{2,79} = 0.0117$; $P = 0.988$). *Table 1* comprises an overview of the mean number of pellets taken and the mean number of lick responses performed by APP23 mice and their wild-type littermates, per age category. Two-way RM ANOVA with factors genotype and day/night (i.e. accumulated number of responses during light or dark periods) revealed significant differences between APP23 and wild-type animals, in eating behavior as well as in drinking behavior (2-way RM ANOVA; eating; $F_{1,83} = 5.799$; $P = 0.018$, drinking; $F_{1,83} = 5.963$; $P = 0.017$). This analysis also confirmed an effect of day and night on food and water consumption (eating; $F_{1,83} = 322.634$; $P < 0.001$, drinking; $F_{1,83} = 540.941$; $P < 0.001$), but no significant interactions (eating; $F_{1,83} = 2.633$; $P = 0.108$, drinking; $F_{1,83} = 2.233$; $P = 0.139$).

Additional extracted eating and drinking parameters are also overviewed in *Table 1*. The eating and drinking profile analyses revealed no significant differences in average meal size or size of drinking sessions between both genotypes and age groups. There was however a genotype-dependent difference in the number of drink sessions performed (2-way ANOVA; number of drink sessions; $F_{2,79} = 5.636$; $P = 0.020$) and an effect of age on the number of meals (number of meals; $F_{2,79} = 3.859$; $P = 0.025$). Age also had an effect on the duration of both eating and drinking episodes and the inter-meal intervals (meal duration; $F_{2,79} = 4.552$; P

= 0.013, drink duration; $F_{2,79} = 5.933$; $P = 0.004$, inter-meal interval; $F_{2,79} = 3.763$; $P = 0.027$). Moreover, we discovered significant differences between both genotypes in the inter-meal intervals and the interval lengths between subsequent drink sessions (inter-meal interval; $F_{1,79} = 4.562$; $P = 0.036$, inter-drink session interval; $F_{1,79} = 10.807$; $P = 0.002$). APP23 mice quicker initiated a subsequent meal and also drink session after a preceding meal or drink session in comparison with wild-types (*Table 1*).

The monitoring of the evolution of body weight in male APP23 and wild-type mice showed significant differences between both genotype groups (2-way RM ANOVA; $F_{1,1696} = 36.393$; $P < 0.001$). At weaning, i.e. the age of 4 weeks, wild-type and APP23 mice weighed the same (post-hoc Tukey HSD test; 4 weeks: $P = 0.173$). However, from the age of 4.5 weeks onwards, APP23 males' weights were significantly lower and the difference increased with age (post-hoc Tukey HSD test; 4.5 weeks: $P = 0.021$; 5 – 5.5 weeks: $P = 0.005$; 6 – 108 weeks; $P < 0.001$) (*Figure 1*).

Olfaction appeared intact in male APP23 mice of 6-8 weeks, 3, 6 and 12 months of age. Two-way ANOVA did not reveal significant genotype-dependent differences in the latencies to enter the target (i.e. the food baited) arm (2-way ANOVA; $F_{1,142} = 2.474$; $P = 0.118$), in the number of entries in the target arm over the total number of entries in the different zones ($F_{1,145} = 1.240$; $P = 0.267$), in the percentage of time spent in the target arm ($F_{1,145} = 0.0116$; $P = 0.914$), or in the total recording duration, which was a consequence of the time a mouse needed to locate the food ($F_{1,145} = 0.0982$; $P = 0.754$). Neither was there an effect of age nor significant interactions between genotype and age.

Discussion

The number of pellets taken and the number of performed licking responses was monitored during a 1-week registration period and revealed male APP23 mice to eat and drink more than their wild-type littermates. Food and water intake in mice follow diurnal patterns, which is also recognizable in the present analysis of eating and drinking data. The extended meal and drink pattern analysis shows genotype differences in the number of drink sessions and the intervals between subsequent meals and drink sessions, with APP23 mice performing more drink sessions and overall displaying shorter breaks between meals and drink episodes compared with their wild-type littermates. Considering this increased food and water intake in APP23 mice, it is surprising that they weigh less in comparison to wild-type littermates from the age of 4.5 weeks onwards. Nevertheless, these findings confirm the increased eating behavior and reduced body weight of the double transgenic APP/PS1 mice recently reported by Pugh et al. (2007). They determined average 24-h food intake during a period of 3 days by weighing the food pellets in the home cage and employed LABORAS to detect increased frequency and duration of feeding bouts. Body weights of APP/PS1 mice were evaluated at the age of 2, 5 and 10 months, in contrast to our longitudinal follow-up in the APP23 model.

Decreased body weight in the AD mouse models accurately models the weight loss, often exhibited in dementing patients (Gillette-Guyonnet et al., 2000; Poehlman & Dvorak, 2000; White et al., 1994). Low body weight in AD is associated with mesial temporal cortex atrophy, a region of the central nervous system which is involved in the control of feeding behavior, confirming a possible morphological basis for the association between central nervous system pathology and weight loss in AD patients (Grundman et al., 1996). Several hypotheses for the observed weight loss in AD patients, have been postulated, among which failure of body weight regulation, elevated resting energy expenditure, hypermetabolism and

self-feeding difficulties, for example due to olfactory dysfunction (Keller et al., 2003; Grundman et al., 1996). Yet the alterations in eating and drinking behavior in the APP23 model are not attributable to a disturbed sense of smell, since the olfactory investigation demonstrated intact function. Evidence for elevated energy needs, came from a study revealing that AD patients tended to weigh less, but actually required more calories (Wolf-Klein et al., 1995). Wang et al. (2004) also found AD patients, who presented with body weight loss, to consume more calories per body weight kilogram per day. Though the number of studies is limited, not all previous reports confirm these findings (for reviews see: Mazzali et al., 2002; Poehlman & Dvorak, 2000). Nevertheless, the present study supports the hypothesis of the existence of a hypermetabolic state in AD. Moreover, Wolf-Klein et al. (1992) reported analogous increases in food intake with concomitant weight loss in AD patients.

Hyperthyroidism is a hypermetabolic state, characterized by hyperphagia and weight loss, and accompanied by increased production of reactive oxygen species (Mayer et al., 2004). Several studies found evidence for the presence of hyperthyroidism in AD patients and the prospective Rotterdam study also suggested that subclinical hyperthyroidism in the elderly increases the risk of developing AD and other forms of dementia (Dobert *et al.*, 2003, Kapaki *et al.*, 2006, Kalmijn *et al.*, 2000). Recent studies moreover confirmed lower thyroid-stimulating hormone levels to be a risk and even predictive factor of AD (van Osch *et al.*, 2004, Annerbo *et al.*, 2006). Reports were however inconsistent, with studies suggesting that subclinical hypothyroidism relates to dementia (for review see Davis *et al.*, 2003). On the other hand, some researchers did not found any evidence for an association between thyroid abnormalities and AD (Lopez *et al.*, 1989, de Jong *et al.*, 2006). Though thyroid status might be relevant to AD pathogenesis, until now it remains unclear whether thyroid dysfunction

results from or contributes to AD pathology. In addition, thyroid hormones are known to induce oxidative stress, to which mitochondrial structures are particularly susceptible (for review see: Venditti & Di Meo, 2006). Mitochondrial damage may play a pivotal role in cell death, which might lead to synaptic failure and neuronal degeneration occurring in AD (Eckert et al., 2003). Accumulated amyloid in the mitochondrial matrix has been demonstrated to impair energy metabolism and exaggerate neuropathological changes, as well as learning and memory deficits in transgenic AD mouse models (for review see: Chen et al., 2006).

A final assumption we would like to address is insulin deregulation leading to the development of a hypermetabolic state. However, in AD patients such state has to our knowledge never been related to disturbances in insulin regulation. Nonetheless, AD is associated with insulin deficiency, whereas insulin in the brain regulates food intake, body weight and energy balance by interacting with a variety of neuropeptides, such as leptin, cholecystokinin, neuropeptide Y and glucocorticoids (Stockhorst et al., 2004; for review see: Sun & Alkon, 2006). Chronic infusion of insulin into the ventricular system reduces food intake and body weight (Brief & Davis, 1984), which is in line with our findings of hyperphagia, but does not explain the decreased body weight of the APP23 mice. Interestingly, the effects of centrally administered insulin have been reported to vary according to body weight, with lean animals exhibiting the greatest changes in food intake (Ikeda et al., 1986). Whether such differential effects of insulin deficiency underlie the changes in the APP23 model still remains to be elucidated.

Conclusion

This is the first report, evidencing the existence of changes in eating as well as drinking behavior in a single transgenic APP overexpression model. APP23 mice display increased food and water intake and alterations in meal and drink patterns. Surprisingly, from the age of 4.5 weeks onwards, their body weight is significantly lower in comparison to their wild-type littermates. Our results may support the hypothesis of the existence of a hypermetabolic state in AD. Higher energy requirements might explain higher nutritional intake in combination with low body weight. Given the present findings and many other parallels between the transgenic APP23 mice and the clinical situation, the model becomes an even more promising and valuable animal model for AD-related research.

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Acknowledgements

This work was financed by the Fund for Scientific Research – Flanders (FWO, grant G.0038.05), agreement between Institute Born-Bunge and the University of Antwerp, the Medical Research Foundation Antwerp, Neurosearch Antwerp, and the Thomas Riellaerts Research Fund.

Table 1 – Vloeberghs *et al.* – Eating & drinking behavior in the APP23 model

Table 1 **Eating and drinking parameters (± SEM) of naive male APP23 mice and wild-type littermates at 3 different ages during a 1-week registration period.**

	3 months		6 months		12 months	
	Wild-type *(n = 14)*	**APP23** *(n = 13)*	**Wild-type** *(n = 13)*	**APP23** *(n =13)*	**Wild-type** *(n = 17)*	**APP23** *(n = 15)*
EATING BEHAVIOR						
Total food intake (number of pellets taken)	1991 ± 138	2193 ± 250	1872 ± 91	2200 ± 110	1720 ± 84	2012 ± 143
Meal size (number of pellets taken)	12.23 ± 1.00	26.78 ± 13.90	11.72 ± 0.50	12.66 ± 0.60	12.19 ± 0.43	11.90 ± 0.60
Total number of meals	149.57 ± 5.00	148.31 ± 8.81	147.00 ± 4.31	161.77 ± 4.24	130.41 ± 6.53	144.73 ± 6.97
Meal duration (minutes)	10.72 ± 1.32	11.32 ± 1.00	8.91 ± 0.40	10.74 ± 0.64	8.77 ± 0.47	8.71 ± 0.42
Inter-meal interval (minutes)	54.74 ± 1.80	55.80 ± 3.86	57.50 ± 2.30	50.22 ± 1.54	68.00 ± 4.58	56.55 ± 3.68
DRINKING BEHAVIOR						
Total water intake (number of lick responses)	25864 ± 2631	31523 ± 3248	29122 ± 2134	34938 ± 2825	32305 ± 2949	38791 ± 3479
Size of drink session (number of lick responses)	166.55 ± 16.19	184.14 ± 18.11	182.32 ± 11.66	202.77 ± 18.80	185.42 ± 14.55	203.21 ± 14.65
Total number of drink sessions	153.57 ± 8.30	168.54 ± 6.76	157.39 ± 5.60	176.00 ± 10.80	172.18 ± 9.46	188.00 ± 7.83
Drink session duration (minutes)	12.28 ± 0.87	13.32 ± 0.88	10.55 ± 0.70	12.21 ± 1.62	9.73 ± 0.94	9.31 ± 0.62
Inter-drink session interval (minutes)	54.13 ± 4.30	44.52 ± 2.03	51.72 ± 1.87	45.59 ± 2.93	47.97 ± 2.66	41.21 ± 1.99

Figure 1 – Vloeberghs *et al.* – Eating & drinking behavior in the APP23 model

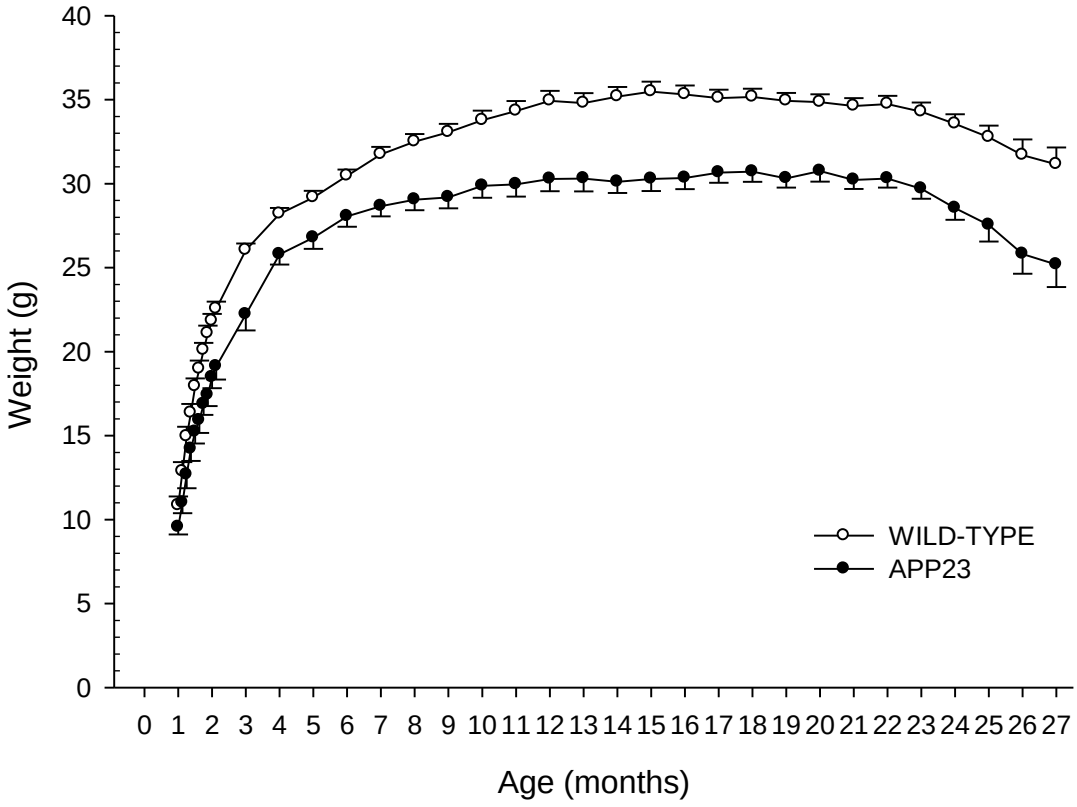

Figure 1: Growth curves. **This graph represents the mean body weights (± SEM) of male APP23 mice (black symbols) and wild-type littermates (white symbols) from weaning until the age of 108 weeks. At the age of 4 weeks, wild-type and APP23 mice weighed the same (post-hoc Tukey HSD test; 4 weeks: *P* = 0.173), whereas from the age of 4.5 weeks onwards, APP23 mice weighed significantly less compared to their wild-type littermates (4.5 weeks: *P* = 0.021; 5 – 5.5 weeks: *P* = 0.005; 6 – 108 weeks; *P* < 0.001). For reasons of clarity, asterisks indicating significant differences between both genotype groups were not included in the figure.**