Careful adjustment of food deprivation levels is important when assessing motivation in obese transgenic animals

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Huntington disease (HD) is an autosomal dominantly inherited neurodegenerative disease with a prevalence of 6 per 100 000 in Europe and North America. Development of HD is dependent on a single mutation that results in the extension of the CAG repeat sequence present in the gene for the Huntingtin protein. The major neuropathological hallmark of the disease is a gradual degeneration of the basal ganglia, and HD patients display a range of symptoms that can be grouped into motor, psychiatric, cognitive and metabolic symptoms. There is currently a growing interest for the cognitive symptoms of HD, as they have been found to be present at early stages of the disease, and might thus prove to be of importance when tracking disease progression and treatment effects.

Many tests for cognitive function in rodents are based on food depriving the animals and having them perform certain tasks to retrieve food rewards. For such tests, animals are typically food deprived until they reach a specific body weight. However, the standard protocols might not be entirely suitable for HD models, due to the metabolic disturbances that are often present. For example, animals that express the full-length mutated human protein often show an increased body weight, due to increased amounts of adipose tissue. It is possible that depriving these animals and their wild type (WT) counterparts to the same relative body weight would lead to different hunger levels. Although all behavioral protocols might not be dependent on animals being equally hungry, this is still a preferred situation, as the effect that motivational differences can have on performance is not known for many tests.

Animals' food interest can be assessed by measuring the amount of food consumed during a brief period of free access. In HD research, such tests have been used to match animals' food consumption rates when running operant conditioning tests [1,2] in order to ensure equal hunger and food interest. Thus, we have investigated, whether this food deprivation strategy is suitable for our recently established BACHD rat model of HD. These rats carry a large construct containing the full-length gene for human mutant Huntington, with its endogenous regulatory sequences [3].

First, we concluded that although there was no difference in body weight, BACHD rats carried significantly more adipose tissue compared to WT rats. Further, apart from a brief period of over-eating at young ages, BACHD rats typically ate less food compared to WT rats. We then studied WT and BACHD rats' performance in a progressive ratio test, using different food deprivation strategies. In the progressive ratio test, rats are prompted to lever-push for a small food reward. During a test session, the number of lever pushes required for reward delivery gradually increases, and rats eventually start to lose interest. A common measurement of the rats' motivation is the number of rewards they obtain before taking a break of a specified minimum duration. When BACHD and WT rats were both deprived to 85% of their respective free-feeding body weights, BACHD rats were clearly less motivated than WT rats in the progressive ratio test. In HD research, such a phenotype is of interest, as it could be an indicator of apathy, a common symptom among HD patients. However, BACHD rats also responded with more pronounced drops in motivation when being fed a specified amount of food before the daily test session. In addition, they consumed less food compared to WT rats when given free access for a brief period of time. Both these phenotypes could be indicators of a lower hunger level, which naturally would reduce the rats' interest in lever pushing for a food reward.

To evaluate the use of the aforementioned food deprivation strategy, the food deprivation level of the WT rats was then adjusted so that their food consumption rate was equal to that of the BACHD rats. At that point,

BACHD and WT rats showed equal motivation in the progressive ratio test, and also responded equally to the prefeeding tests. Thus, the initial motivational deficit that was present among BACHD rats appeared to be the result of using a suboptimal food deprivation strategy, leading to BACHD rats being less hungry than WT rats. The study highlights the need for careful adjustments of food deprivation levels when working with obese animals, and supports the use of brief food consumption tests for minimizing motivational differences due to differences in hunger levels.

Ethical statement

All experimental procedures were approved by the commission for animal experiments at the Regierungspräsidium Tübingen in accordance with the guidelines of the German animal welfare act.

References

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