Motor assessment in transgenic Tau mice

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Tau is a microtubule-associated protein functionally known to bind microtubules and to be critical in the process of neuronal outgrowth and axonal integrity [1-4]. Intracellular accumulation of filamentous tau inclusions are neuropathological hallmarks of neurodegenerative disease known as tauopathies which are associated with the progressive loss of cognitive, behavioural and motor functions [5-7]. The discovery that mutations in the tau gene can cause a familial form of fronto-temporal dementia with parkinsonism linked to chromosome 17, (FTDP-17) has established the central role of tau dysfunction in neurodegenerative disease [8,9]. Several transgenic mouse lines over-expressing mutant human tau in neurons and glial cells have now been expressed [10].

The aim of this study was to provide a behavioural characterization of one such transgenic mouse line (line 66) as a potential model for investigating the role of tau in neurodegeneration. These transgenic mice, bred on a NMRI background strain, exhibit a progressive and age-related deterioration in motor performance and learning skills, features common in the tauopathies. One phenotypes of line 66 mice is a palsy-like shaking or wobbling of the body which emerges at about 7-9 months of age. Line 66 mice were allocated to two different groups depending on whether they visibly displayed this phenotype ("wobblers") or not ("non wobblers"). Using a battery of sensorimotor tasks, we investigated the differences in sensorimotor skills, gait and motor learning for line 66 groups compared with wild-type control mice. The following tests were used: the Rotarod test to assess motor learning and motor coordination; the balance beam test to examine sensorimotor coordination and balance of mice and an automated Catwalk analysis to provide a large number of gait parameters (both static and dynamic). In the Rotarod task, mice were placed on an accelerating rod and the latency to fall from the rod recorded for a maximum period of 300 sec. In the balance beam test, mice had to climb six beams differing in both thickness (28-, 11- or 5-mm) and shape (square or round) in a maximum time of 30 sec. The latency to reach the upper end of a beam, at inclination of 30°, was the dependent measure. In the Catwalk mice had to traverse from one end to the other of a glass plate. With this computer-assisted method of locomotor analysis, it is possible to quantify several gait parameters, including the duration of different phases of the step cycle and the pressure applied during locomotion.

Using the Catwalk system, we have quantified a large number of gait parameters for line 66 and wild-type mice. Marked groups differences were noted on the static parameters; the hindlimb base-of-support was wider in wild-type mice compared to line 66 groups. A feasible explanation for the observed differences might be that line 66 mice tend to hold their hind legs in a crossed position close to their bodies. Also, as shown in relative paw placement results, line 66 have a propensity to place their hind paws in front the previously placed ipsilateral forepaws. Inter-limb coordination is a key characteristic of locomotion and therefore the parameters relating to coordination are of particular interest. All strains used the two alternate patterns (i.e. Aa and Ab) and the two cruciate patterns (i.e. Ca and Cb) with a preference for the Ab pattern. In particular, the higher proportion of wobblers using the Ab step sequence pattern compared with wild type mice might be as accounted for by an adjustment in walking balance. The shaking of the body, in line 66 wobblers, makes it extremely unstable for the mouse to walk with a simultaneous swing of one body side and so the use of left front and right hind paws followed by right front and left hind paws (Ab) represents the most stable way for these mice to walk. Rotarod and balance beam tests revealed that line 66 mice developed significant motor impairments compared with non transgenic age-matched control mice. It was possible to also detect motor and sensory motor differences within the same genotype. In both tests, wobblers showed a worse performance relative to the non wobbler group indicating a higher deficit in coordination and balance skills.

Line 66 mice, therefore, offer relevant information as a simplified model for human tauopathies and, together with other model systems, it may assist in our understanding of the role of tau in neurodegeneration and in the development of therapeutic agents.

References

1. Brandt, R., Lee G. (1993).The balance between tau protein's microtubule growth and nucleation activities: implications for the formation of axonal microtubules. *J. Neurochem*. **61**, 997–1005.
2. Brandt, R., Lee G. (1993). Functional organization of microtubule-associated protein tau. Identification of regions which affect microtubule growth, nucleation, and bundle formation in vitro. *J. Biol. Chem*. **268**, 3414–3419.
3. Cleveland, D.W., Hwo, S.Y., Kirschner, M.W. (1977). Physical and chemical properties of purified tau factor and the role of tau in microtubule assembly, *J. Mol. Biol.* **116,** 227– 247.
4. Weingarten, M.D., Lockwood, A.H., Hwo, S.Y., Kirschner, M.W. (1975). A protein factor essential for microtubule assembly, *Proc. Natl. Acad. Sci. USA* **72**, 1858–1862.
5. Spillantini et al. (1997). Familial multiple system tauopathy with presenile dementia: a disease with abundant neuronal and glial tau filaments, Proc Natl Acad Sci U S A. **94,** 4113-8.
6. Perry, R.J., Hodges J.R. (1999). Attention and executive deficits in Alzheimer's disease: a critical review. *Brain* **122**, 383-404.
7. Swartz, J.R., Miller, B.L., Lesser, I.M., et al. (1997). Behavioral phenomenology in Alzheimer's disease, frontotemporal dementia, and latelife depression: a retrospective analysis. *J Geriatr Psychiatry Neurol.***10**, 67-74.
8. Poorkaj, P., Bird, T.D., Wijsman, E., Nemens, E., Garruto, R.M., Anderson, L. et al. (1998).Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol*. **43,** 815–25.
9. Spillantini, M.G., Crowther, R.A., Kamphorst, W., Heutink, P., van Swieten, J.C. (1998) Tau pathology in two Dutch families with mutations in the microtubule-binding region of tau, *Am. J. Pathol.* **153**, 1359–1363.
10. Lewis, J., McGowan E., Rockwood, J., Melrose, H., Nacharaju, P., Van Slegtenhorst, M., Gwinn-Hardy, K., Paul Murphy, M., at al. (2000). Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein, *Nat. Genet*. **25,** 402–405.