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Negative results

# Neuronal histamine production remains unaltered in Parkinson's disease despite the accumulation of Lewy bodies and Lewy neurites in the tuberomamillary nucleus

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#### Abstract

Neuronal histamine production in the hypothalamic tuberomamillary nucleus (TMN) was hypothesized to change significantly in Parkinson's disease (PD) in relation to the accumulation of Lewy bodies/Lewy neurites (LBs/LNs). We measured the messenger ribonucleic acid (mRNA) levels of histidine decarboxylase (HDC), the key enzyme of histamine production, and the amount of LBs/LNs in the TMN by quantitative in situ hybridization and immunocytochemistry in postmortem human brain material of clinical PD (CPD), preclinical PD, and control subjects. No significant difference of histidine decarboxylase mRNA levels was observed among different clinical or Braak-PD stages, in spite of the strong accumulation of LBs/LNs in the TMN of clinical PD patients. We conclude that neuronal histamine production remains largely unaltered in PD despite the abundant LB/LN accumulation in the TMN. © 2012 Elsevier Inc. All rights reserved.

Keywords: Neuronal histamine; Histidine decarboxylase; Tuberomamillary nucleus; Parkinson's disease; Lewy body; Lewy neurites

## 1. Introduction

Neuronal histamine is exclusively produced in the hypothalamic tuberomamillary nucleus (TMN), which projects to a large number of brain areas and participates in a number of functions including the sleep-wake cycle, sensory and motor adjustment, cognition, attention, learning, and memory, all of which are observed to be altered in Parkinson's disease (PD) (Haas and Panula, 2003). In addition, abundant accumulation of the characteristic neuropathological PD lesions, i.e., Lewy bodies (LBs) and Lewy neurites (LNs) are found in the TMN of PD patients, which implicates functional changes of this nucleus (Braak et al., 2003). Furthermore, animal experiments also showed that endogenous histamine caused death of dopaminergic neurons in the substantia nigra (SN) and PD-like behavior, in an early stage (Liu et al., 2007). These data strongly suggested changes in TMN histamine production in the course of PD. Therefore we measured the messenger ribonucleic acid (mRNA) levels of the key enzyme of histamine production, histidine decarboxylase (HDC), and the amount of LBs/LNs in the TMN in postmortem human brain material of PD patients in different clinical or Braak-PD-stages to test this hypothesis.

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# 2. Methods

Formalin fixed, paraffin-embedded human brain samples were obtained from the Netherlands Brain Bank (Director Dr. I. Huitinga), with permission for a brain autopsy and for the use of the brain material and clinical data for research. In total 15 subjects with different stages of PD (9 clinical PD patients [CPD]; 6 preclinical PD subjects [PPD]) and 15 matched controls were studied. The HDC-mRNA levels in the TMN were measured by quantitative in situ hybridization (ISH), and the amount of LBs/LNs were determined by double staining of  $\alpha$ -synuclein and thionine in the TMN and image analysis (for details see supplementary material).

## 3. Results and discussion

There were no significant differences in HDC-mRNA levels among the PPD, the CPD, and the control subjects ( $p \ge 0.171$ ), despite that the CPD group showed significant abundant staining of LBs/LNs in the TMN compared with the PPD or controls (p < 0.005). No significant correlation was found between the HDC-mRNA levels and the amount of LBs/LNs in any groups. Moreover, the HDC-mRNA levels showed no significant differences among different Braak PD stages in any groups ( $p \ge 0.439$ ).

This is the first quantitative study determining the HDCmRNA expression in the TMN in different PD stages. The unaltered HDC-mRNA levels in PD patients, either when they were grouped by clinical or preclinical PD, or by neuropathological Braak PD staging, together with the significant accumulation of LBs/LNs in CPD patients, does not support the literature that suggested changed TMN activity, i.e., an increased endogenous neuronal histamine level, that would be involved in the degeneration of the substantia nigra in early PD stages (Liu et al., 2007), nor that the later strong accumulation of LBs and LNs in late PD stages would be accompanied by TMN neurodegeneration (Braak et al., 2003). It should be noted, however, that increased histamine concentrations and a significantly higher density of histamine-containing nerve fibers have been observed in PD patients, indicating local changes of histaminergic neurotransmission in some areas of termination of the histaminergic system (see supplementary references). Our findings also implicate that the PD lesions may protect the TMN cells rather than cause degeneration.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging. 2011.01.004.

#### References

- Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen-Steur, E.N., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211.
- Haas, H., Panula, P., 2003. The role of histamine and the tuberomamillary nucleus in the nervous system. Nat. Rev. Neurosci. 4, 121–130.
- Liu, C.Q., Chen, Z., Liu, F.X., Hu, D.N., Luo, J.H., 2007. Involvement of brain endogenous histamine in the degeneration of dopaminergic neurons in 6-hydroxydopamine-lesioned rats. Neuropharmacology 53, 832–841.