

## EARLY NEURODEGENERATION IN THE BRAINS OF YOUNG DRUG ABUSERS: AN INVESTIGATION OF TAU PROTEIN

### Researchers

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### Aim

1. To investigate the relationship between opiate abuse and premature brain damage related to deposits of insoluble Tau protein.
2. To investigate possible causative factors associated with Tau deposition.

### Project Outline/Methodology

Hyperphosphorylated Tau (hTau) and beta amyloid ( $\beta$ A) are insoluble brain proteins which accumulate characteristically in Alzheimer's disease (AD). We have shown previously that elevated levels of hTau are found in the brains of drug users (DUs). In this study, post mortem brains were examined from 39 DUs, and compared with 5 AD subjects (expected very heavy load of hTau and  $\beta$ A) and 30 age matched control cases (expected low load but increasing with age).

The amount and location of hTau and  $\beta$ A were determined in each case by special staining methods. These results were correlated with investigation of other factors in the brain thought to contribute to the development of AD, such as brain vascular disease and the level of inflammation in brain tissue.

### Key Results

We confirmed that hTau is significantly raised in DU brains compared with age matched controls, and reaching the levels seen in much older non-demented elderly brains but not those present in AD. hTau accumulated at a faster rate in DU brains than in controls and was found principally in temporal and frontal lobes, areas concerned with memory and personality functions. The type of hTau seen in DU brains resembled that seen in AD. GSK-3, an enzyme promoting hTau formation, was elevated in DU brains. More  $\beta$ A was also present in DU brains but the difference from controls was not significant and there was no evidence of significant association between the two insoluble proteins in individual brains. While there was a significant correlation between hTau accumulation in DU brains and (i) the degree of activation seen in microglial cells (the immune cells

of the brain) and (ii) breakdown of the blood brain barrier, there was no link with other vascular pathology.

### Conclusions

DUs are at risk of developing AD-like brain changes that are likely to predispose them to early onset dementia. This is associated with neuroinflammation.

### What does this study add to the field?

This study confirms and expands our previous finding of early neurodegeneration in DUs and establishes a time sequence for the increasing damage. It also identifies a direct relationship with activation of the brain's own inflammatory cells, which further underlines the similarity with early stages of AD. However the accumulation of hTau and  $\beta$ A appear to be independent of each other in an individual case.

### Implications for Practice or Policy

Drug abusers should be monitored for early onset of AD-like disorders. The involvement of inflammatory changes in these early stages suggests (i) it may be useful to treat older DUs to protect brain function (ii) that DU represents a scientific opportunity to investigate the earliest stages of AD-like brain changes with the objective of prevention rather than cure.

### Where to next?

To widen the investigation of early stages of neurodegeneration in other groups of individuals to establish whether neuroinflammation is a universal setting for premature neurodegeneration.

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