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DOSE CHRONIC ANTI-CHOLINERGIC TREATMENT ALTER PATHOLOGY OF A MOUSE MODEL OF TAUOPATHY?

Hypothesis / aims of study

Anti-cholinergic drugs and drugs with anti-cholinergic properties are widely and frequently used. It is well known that these drugs impair cognitive function. In a recent report, comparing with control groups without , score of reaction time, attention, spatial memory (immediate, delay), word fluency, visual space perception, and recall (word, story, name) decreased in groups that take anti-cholinergic drugs, although score of word memory (immediate, delay, implicit) and logical reasoning unchanged. The mechanism of anti-cholinergic drug-induced cognitive impairment has been assumed to be functionally reduced acetylcholine (ACh) neurotransmission in the central nervous system. However, some reports have indicated that anti-cholinergic drugs might occur neurodegenerative change and enhance pathology of neurological disease. Among anti-cholinergic drugs, there are drugs for the treatment of enuresis and drugs for the treatment of overactive bladder. Although most of these drugs are organ- and/or receptor-specific and have less central anti-cholinergic action except drugs with anti-cholinergic properties for enuresis, we clinically experience some cases with drug-induced parkinsonism, cognitive impairment and psychosis after taking these drugs. However, there was no report to evaluate whether these anti-cholinergic drugs occur neurodegenerative change and enhance pathology of neurological disease or not. Therefore, we investigate the influence of anti-cholinergic drugs for enuresis and overactive bladder on neurodegeneration by using tauopathy model mouse.

Study design, materials and methods

Human tau transgenic mouse was studied as a model of dementia and related tauopathies. Mice were treated orally on everyday from 2-3 months to 10 months old. Mice were randomized to receive 5 mg/kg propiverine (PP), 1.5 mg/kg trihexyphenidyl (TP) and placebo. Trihexyphenidyl, which is preferentially used for the treatment of Parkinson's disease and has central anti-cholinergic action, was used to compare with propiverine, which is used for the treatment of overactive bladder and has a less central anti-cholinergic action. Surviving mice were dissected and mice brain was analyzed pathologically and chemically. Furthermore, to investigate the effects of these anti-cholinergic drugs on systemic inflammation and to asses the effects of anti-cholinergic drugs on neurodegeneration, we administered TP or PP to model mice in which we had artificially induced inflammation by lipopolysaccharide injection.

Results

Tau pathology, synaptic loss, and neurodegeneration in the hippocampal region, as well as tau insolubility and phosphorylation, markedly and significantly increased in chronically TP-treated mice and mildly increased in chronically PP treated mice. Furthermore, immunohistochemical analysis revealed microglial proliferation and activation particular in chronically TP-treated mice. Moreover, anti-cholinergic drugs, in particular TP, increased interleukin-1β expression in both the spleen and brain of the tauopathy model mice that intraperitoneally injected with lipopolysaccharide to induce systemic inflammation. Interestingly, these alterations were more strongly observed in chronically TP-treated mice than in chronically PP-treated mice, consistent with the level of central anti-cholinergic action.

Interpretation of results

Markedly neurodegenerative change occurred in chronically TP-treated model mice, suggesting that drugs with central anti-cholinergic action may induce neurodegenerative change. In chronically PP-treated model mice, mildly neurodegenerative change occurred, suggesting large amount of and long-term administrating drugs with peripheral anti-cholinergic action may also induce neurodegenerative change by suppressing a ACh-dependent anti-inflammatory system peripherally.

Concluding message

Anti-cholinergic drugs not only impair cognitive function by decreased central ACh neurotransmission, but also induce neurodegeneration and accelerate pathology of neurological disease by over-suppressing a peripheral ACh-dependent anti-inflammatory system. This effect is consistent with the level of central anti-cholinergic action. Anti-cholinergic drugs, even in drugs with mainly peripheral anti-cholinergic action, should be less readily, chronically and abundantly prescribed to reduce the risk of cognitive impairment and neurodegenerative change.

Disclosures

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