

EFFECTS OF ACETYLCHOLINESTERASE INHIBITOR ON OVERACTIVE BLADDER [CAUSED] BY CEREBRAL INFARCTION IN RATS

Hypothesis / aims of study

There are two major diffuse modulatory cholinergic systems in the brain, one of which is called the basal forebrain complex, and the other is composed of acetylcholine (ACh)-utilizing cells in the pons and midbrain tegmentum. The cholinergic pathway between the frontal cortex and the basal nucleus has been reported to play a part in the forebrain inhibitory mechanisms involved in the voiding reflex (1). Damage to this inhibitory pathway enhances the voiding reflex, resulting in overactive bladder (OAB). The latter cholinergic system has been implicated in regulating sleep and consciousness, and also contributing to excitatory control of the voiding reflex. These reports indicate that the central cholinergic systems play an important role in the regulation of the voiding reflex. Recent reports indicate that dysfunction of the intra-cerebral ACh system occurs in cerebral ischemia (2). Therefore, we evaluated the function of the ACh system in the brain following cerebral ischemia, and examined whether reactivation of this regulatory system using acetylcholinesterase inhibitor could improve OAB.

Study design, materials and methods

Left middle cerebral artery occlusion (MCAO) was performed in female Sprague-Dawley rats under halothane anesthesia. Cholinesterase (ChAT) activities after MCAO were assayed to assess the damage to cholinergic neurons. The rats were killed by decapitation 1, 5, and 24 hours after MCAO. ChAT activities in the bilateral cortex, hippocampus, and pons were calculated by measuring the conversion of 1- [¹⁴C] acetyl-coenzyme A to [¹⁴C] acetylcholine. The effects of intravenous (iv) or intracerebroventricular (icv) donepezil hydrochloride, a centrally acting choline esterase inhibitor, [on cystometrography] were investigated in conscious sham operated (SO) and cerebral infarcted (CI) rats. The dose concentrations for iv and icv administration were 5x10⁻⁷mg/kg to 5x10⁻¹mg/kg, and 5x10⁻⁷mg/ml to 5x10⁻⁴mg/ml (5 µl/rat), respectively.

Results

After cerebral infarction, the highest increase in bladder capacity was attained at 5x10⁻⁵mg/kg of Donepezil hydrochloride concentration given intravenously with a change of 52.8% (p<0.05). In the cases of intra-ventricular Donepezil hydrochloride administration, the highest increase in bladder capacity was at the concentration of 5µl of 5x10⁻⁵mg/kg with a change of 95.8% (p<0.01). In any cases micturition pressure was no apparent changes. The changes of cholinesterase activity gradually decreased (p<0.05).

Interpretation of results

Bladder overactivity caused by cerebral infarction is thought to be mediated by downregulation of M1 muscarinic inhibitory mechanism. By Donepezil hydrochloride as a centrally acting choline esterase inhibitor, the muscarinic inhibitory mechanism downregulated by cerebral infarction was activated, and the bladder capacity was thought to be increased.

Concluding message

Due to the upregulation of the M1 muscarinic inhibitory mechanism by Donepezil hydrochloride [OR- Due to Donepezil hydrochloride's upregulation of the M1 muscarinic inhibitory mechanism, bladder overactivity following cerebral infarction was thought to be improved.

References

1. Forebrain muscarinic control of micturition reflex in rats. *Neuropharmacol*, **41**: 629 2001.
2. The disruption of spinal cognition and changes in brain amino acid, monoamine and acetylcholine in rats with transient cerebral ischemia. *Brain Research* 709, 163-17.