Cholinergic system and cholinesterase inhibitors

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Therapy targeting the cholinergic system: Cholinesterase inhibitors have observed the failure of the ascending cholinergic system of the brain. There are both marked reduction and neuronal dropout in synaptic densities in the projections from cholinergic neurones located in substantia innominata of the basal forebrain, which includes the nucleus basalis of Meynert, which projects to all cortical areas, and the septal nuclei, projecting to the hippocampus. This is hypothesised to be on the basis of that there are less cell loss and preservation of the post-synaptic cholinergic receptors. The mainstay of treatment for the cognitive symptoms of Alzheimer’s Disease is aimed at addressing the cortical and limbic cholinergic deficit. At present, there are three agents which are commonly used: donepezil, galantamine and rivastigmine. A fourth ChEI, tacrine, is not favourable because of liver enzyme elevations observed in up to 40-50 per cent of patients. A fifth, noncholinergicagent, memantine, works throughout the alternative mechanism of N-methyl D aspartate receptor antagonism where glutamate mediatedexcito toxicity is reduced. While this approach has some proven efficacy in moderate to severe Alzheimer’s disease.

Pharmacology of cholinesterase inhibitors: Identification of candidate genes for pharmacogenetic studies. In order for the drug to exert the biological effect, it should first accumulate in the tissues where its pharmacological target examining the drug concentration versus time relationships in an organism mathematical modelling of its absorption from site of administration, its distribution in tissues throughout the body, its metabolism by various enzyme systems and its excretion from the body. Once the drug is concentrated in the tissue, it interacts with the targets through which the

final biological effects are elicited (pharmacodynamic interaction). Specifically, pharmacodynamics describes the concentration of the drugs versus effect relationships in the organism. The targets included in a variety of proteins, such as receptors, enzymes, messengers and transporters ion channels among others. A drug may directly or indirectly interact with DNA or RNA to produce its biological effects. The PK-PD paradigm will now be applied to ChEIs to identify candidate genes for pharmacogenetic studies. Pharmacokinetics of cholinesterase inhibitor drug metabolism is one of the pivotal factors contributing to variability in the PK of ChEIs and other drugs. 35 Donepezil and galantamine are metabolised in the liver by cytochrome CYP3A4 and CYP2D6 enzymes. They undergo the first-hand metabolism. Of the major donepezil metabolites, the CYP2D6 product has the same pharmacological activity to that of the parent compound, while the CYP3A4 metabolite is inactive, Therefore, variation in CYP3A metabolism should play a significant role in the variable clinical effects of donepezil. The main CYP2D6 which is a galantamine metabolite is three times more potent than the parent compound as ChEI and can account for 20 per cent of an oral dose. variation in the CYP2D6 which contributes to the variability in the clinical effect of this drug. Galantamine clearance was found to be reduced by certain percent in metabolisers of CYP2D6. Redundant metabolic pathways, however, including CYP3A4 metabolism, which makes CYP2D6 polymorphism unlikely to Cholinesterase be of consequence in determining the pharmacodynamic profile. rivastigmine does not undergo any significant hepatic microsomal oxidation by CYP enzymes. Instead, it is rapidly and extensively metabolised in the serum and at the site of action by cholinesterases. Following this metabolism, it is quickly by the kidneys.

Pharmacodynamics of cholinesteraseinhibitorsChEIs inhibit and bind to acetylcholinesterase and butyrylcholinesterase , which are enzymes responsible for the hydrolysis of acetylcholine at the synapse. This inhibition increases the amount of synaptic acetylcholine available for nicotinic and muscarinic cholinergic receptor stimulation both centrally and peripherally. Central inhibition is necessary for the cognitive enhancing effects, while the peripheral blockade is thought to be responsible for their dose-dependent side effects BChE and AChE are similar from a molecular perspective and are characterised in terms of their structure-activity relationships The proteins form a central gorge area, within which like two types of molecular binding sites, an anionic and a esteratic site. The central esteratic site is where the hydrolysis of acetylcholine and related molecules takes place, while anionic site binds to the cationicquaternary nitrogen of choline. Similarsites reside peripherally in these enzymes and are responsible for docking and facilitating the transport of acetylcholine to central sites. Theoretically, genetic polymorphisms which causes amino acid changes either at the gorge or peripheral sites would lead to variation in the synaptic acetylcholine levels. Galantamine Donepezil are short-acting competitive inhibitors, which bind to cholinesterases reversabilt. rivastigmine is actively metabolised by cholinesterases thus making it an pseudo-irreversible or intermediate-acting inhibitor. Although all the three drugs have an affinity for both AChE and BChE donepezil and galantamine selectively inhibit AChE to a greater extent thanBChE, whereas rivastigmine has equal affinity for both. Rivastigmine through this additional blockade of BChE, is thought to be of particular benefit in LBDThe ChEIs indirectly increase acetylcholineneuro transmission by facilitating stimulation at nicotinic and muscarinic receptors. Additional to

it galantamine modulates nicotinic receptors-particularly those which comprises of a7 subunits-by binding to an allosteric site and further enhancing cholinergic

Pharmacogenetics of cholinesterase inhibitors: Studies published to dateAPOE and clinical response in AD The APOE gene, is located on chromosome 19q13. it encodes humanapolipo protein E, a membrane bound apoprotein which is involved in lipid metabolism. It has three allelic variants: 12, 13 and 14. These are determined by amino are at positions112, 158. It has a cysteine at both sites which confers the 12 allele, while an arginine at both sites confers the 14 atcodon 158 produce the most frequent allele, 13. In case-control studies, it has consistently been shown that frequency is higher in patients with there is a lower likelihood of developing AD in those with only the 12 allele. Further, there is a gene dosage effect, where14 homozygotes have an earlier age onset than 14heterozygotes, and individuals with the 12 allele has a later age onset. The exact mechanism by which APOE to the pathogenesis of AD is disputed, with alterations in Ab aggregation, synaptic plasticity and lipid metabolism are possibly complementary modes of action. Which are in a small subgroup of Alzheimer’s disease patients. These results have been supported by another study examining cognitive responses to tacrine. Two studies one examining the donepezil response and one examining the galantamine response, shows the opposite effect, where the APOE 14 allele was associated with a stabilised or improved cognitive response. Several negative associations of APOE polymorphism and responses to ChEIs (tacrine, donepezil rivastigmine and galantamine) have also been reported, there is no specific APOE

genotype or allele which predicted clinical response toChEIs. In the large group of patients with diagnosis of amnestic mild cognitive impairment, which thought to be prodromal state of Alzheimer’s disease, the presence of the APOE 14 allele predicted a higher rate in the of conversion to Alzheimer’s Disease in the overall samples at months. were randomised to treatment with donepezil, vitamin E or placebo. Only treatment with donepezil in the first 12 months of the study associated with a conversion rate to Alzheimer’s Disease. The benefit of donepezil extended to 36 months in patients with either one or two APOE Another large RCT rivastigmine to determine if it would delay conversion of MCI toAD demonstrated no efficacy and no differences in relation to APOE allele frequencies between treated- and placebo-arm patients.

Cholinesterase inhibitor therapy: BCHE, APOE executive functions and hippocampal atrophy on magnetic resonance imagingHippocampal atrophy is a magnetic resonance imaging (MRI) finding commonly associated with AD. found no relationship between hippocampal volumes on MRI and APOE genotype in controls and patients with AD although both were independently associated with the diagnosis of AD. Other studies have shown that the APOE 14 allele is associated with rates of hippocampal atrophy in AD. This has been confirmed by more recent from the Alzheimer’s Disease Neuroimaging Initiative (ADNI), which is a large multicentre, prospective study of AD, MCI and normal controls. The APOE allele has been predicted to have more rapid hippocampal atrophy over 12-month period in Alzheimer’s diseased patients. In patients with the diagnosis of MCI, the presence of APOE14 allele was associated with more severe hippocampal atrophy and cognitive dysfunction

than those without this allele. A post-hoc analysis of a large clinical trial of rivastigmine demonstrated that MCI patients in the placebo arm were more likely to convert to AD and have worse hippocampal volumetric loss if they were both APOE 14 and K-variant BCHE carriers, compared with those without the 14 allele who also had at least allele; pharmacogenetics data were not presented for rivastigmine-treated group Given that the hippocampal atrophy can progress over a very short time period in Alzheimer’s disease, it may represent a good endophenotype of the ChEI responsiveness. Although donepezil treatment reduces the rate of improved cognitive and hippocampal atrophy symptoms in AD patients, no interaction between the APOE genotype and donepezil treatment was observed. In a group of MCI patients treated with donepezil, however, a trend was observed whereby hippocampal atrophy rates were slower intreated patients who were APOE carriers. The patients underwent MRI with vascular dementia, cognitive impairment and Alzheimer’s disease are demonstrated that the severity of ischaemic white matter hyperintensities strategically involving the ascending cholinergic pathways was inversely correlated with hippocampal width (measure of atrophy) across all groups. AD patients with moderate to severe ischaemic cholinergic pathway involvement, using a rating scale, performed worse on measures of executive function and visuospatial attention, despite similar measures of memory dysfunction and global impairment compared with of minimal involvement in these pathways. The Alzheimer’s disease patients with involvement of the cholinergic pathways by ischaemic white matter disease on MRI showed less decline over oneyear on tests of executive function and working memory when started on ChEIs, compared with those without this ischaemic burden Similar

responses to ChEIs between the groups were observed for overall cognition, behaviour, function, and on memory, language and isuospatial tasks, that is to say, cognitive tasks probing executive functions appeared to be more sensitive in detecting potential beneficial responses to ChEIsthan those probing other cognitive domains, and may be useful as an endophenotype.