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Genetic Variants of Butyrylcholinesterase and Their Potential Impact on Human Health: A Narrative Literature Review

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A B S T R A C T

Butyrylcholinesterase (BChE) is an enzyme found in plasma and many other parts of the body. It is an enzyme that hydrolyses drugs containing ester bonds, such as drugs acting at the neuromuscular junction and local anaesthetic agent. This literature review aimed to describe genetic variants of butyrylcholinesterase. BChE polymorphisms have been shown to produce enzymes with varying levels of catalytic activity. Analysis of butyrylcholinesterase involves the determination of both enzyme activity and biochemical phenotypes. Phenotype is determined by the use of specific enzyme inhibitors (such as dibucaine or fluoride) that produce phenotype-specific patterns of dibucaine or fluoride numbers. Molecular genetic analyses can determine the true genotypes. In conclusion, genetic variants of human butyrylcholinesterase were one of the first examples in the new field of pharmacogenetics when it was recognized that abnormal response to succinylcholine was due to a mutated enzyme with low binding affinity.

1. Introduction

Butyrylcholinesterase (BChE) is an enzyme that is responsible for breaking down the neurotransmitter acetylcholine and other choline esters in the body.[1-3] It is also known as pseudocholinesterase, plasma cholinesterase, or serum cholinesterase. BChE is produced by the liver and is found in the blood and other tissues. Its main function is to hydrolyze (break down) acetylcholine and other choline esters that are released by nerve cells, which helps to terminate their activity. BChE also has other important functions in the body, including the metabolism of certain drugs, such as succinylcholine, a muscle relaxant used during anesthesia. Genetic variations in the BChE gene can affect the activity and levels of this enzyme, which can have clinical implications for drug metabolism and response.[2]

Examination of the gene for mutations or polymorphisms causing the observed biochemical phenotypes has isolated those responsible for all the most widely known variants. To date, more than 100 polymorphisms have been identified. However, few have been studied fully. In general, butyrylcholinesterase (BChE) polymorphisms have been shown to produce enzymes with varying levels of catalytic activity. The molecular bases of several genetic variants of BChE have been reported, such as the atypical gene, fluoride-resistant gene, silent gene, K variant, J variant and C5 variant. In addition, there are a number of additional BChE polymorphisms

which result in a protein with no enzymatic activity. Enzymes with activity below 10% of the wild type enzyme are called silent variants.[3,4] This literature review aimed to describe genetic variants of butyrylcholinestherase.

Atypical butyrylcholinesterase

Genetic variants of human butyrylcholinesterase were one of the first examples in the new field of pharmacogenetics when it was recognized that abnormal response to the muscle relaxant succinylcholine was due to a mutated enzyme with low binding affinity. Neuromuscular block induced by succinylcholine or mivacurium can be significantly prolonged if the patient has an abnormal genetic variant of butyrylcholinesterase. The trait was called succinylcholine apnea and was shown to be hereditary. A standard dose of succinylcholine paralyzed most individuals for 3-5 minutes, but people with "atypical" butyrylcholinesterase could not breathe for 2 hours. The paralyzed person was awake and could see and hear, but could not breathe without assisted ventilation.[5,6]

Analysis of butyrylcholinesterase involves the determination of both enzyme activity and biochemical phenotypes. Phenotype is determined by the use of specific enzyme inhibitors (such as dibucaine or fluoride) that produce phenotype-specific patterns of dibucaine or fluoride numbers. Molecular genetic analyses can determine the true genotypes. The dibucaine number phenotyping method has proven reliable in identifying the atypical variant as well as carriers of the atypical variant when comparing phenotype to DNA sequencing results.[7]

Among the variants of butyrylcholinesterase is a dibucaine-resistant variant, a result of a point mutation in exon 2 (nt 209A →G), which is manifested by an amino acid change Asp70→Gly (D70G mutation). About 1 out of 2500 Americans is homozygous for the D70G mutation. Dibucaine inhibits normal butyrylcholinesterase to a far greater extent than the abnormal enzyme. The dibucaine number indicates the percentage inhibition of butyrylcholinesterase in the presence of dibucaine.[8-10]

In the case of the usual butyrylcholinesterase genotype (E1uE1u), the dibucaine number is 70 or higher, while in individuals homozygous for the atypical gene (E1aE1a) (frequency in the general population of 1 in 3,500), the dibucaine number is less than 30. In individuals with the heterozygous atypical variant (E1uE1a) (frequency in the general population of 1 in 480), the dibucaine number is in the range of 40 to 60.52, 53 In individuals with the homozygous atypical genotype (E1aE1a), the neuromuscular block induced by succinylcholine or mivacurium is prolonged to 4 to 8 hours, and in individuals with the heterozygous atypical genotype (E1uE1a), the period of neuromuscular block induced by succinylcholine or mivacurium is about 1.5 to 2 times that seen in individuals with the usual genotype (E1uE1u).[9-11]

People who are homozygous for atypical (D70G) or silent butyrylcholinesterase are 100% certain to experience prolonged apnea in response to standard doses of succinylcholine and mivacurium. The longest period of apnea after the administration of succinylcholine was found in patients homozygous for the silent gene (E1sE1s). In those patients, train-of-four stimulation will help in detecting the development of phase II block. The decision of whether to attempt antagonism of a phase II block has always been controversial. However, if the train-of-four ratio is less than 0.4, administration of edrophonium or neostigmine should result in prompt antagonism. The alternative is to keep the patient adequately sedated and maintain artificial ventilation until the train-of-four ratio has recovered to 0.9 or more.[10]

Fluoride resistant butyrylcholinesterase

Fluoride-resistant butyrylcholinesterase variants have also been described. In the case of the fluoride-resistant gene, two amino acid substitutions are possible, namely, methionine for threonine at position 243 and valine for glycine at position 390. The fluoride number indicates the percentage inhibition of butyrylcholinesterase in the presence of fluoride. In the case of the usual butyrylcholinesterase genotype

(E1uE1u), the fluoride number is 60, while in individuals with the homozygous atypical genotype (E1fE1f), the fluoride number is 36. The fluoride-resistant gene was found in 2.7 % of patients with prolonged apnea after administration of succinylcholine.[11,12]

Individuals with homozygous fluoride-resistant genotype exhibit mild to moderate prolongation of succinylcholine-induced paralysis. The heterozygous fluoride-resistant genotype usually produces clinically insignificant prolongation of succinylcholine block unless accompanied by a second abnormal allele or by a coexisting acquired cause of butyrylcholinesterase deficiency.

Silent butyrylcholinesterase

People with silent butyrylcholinesterase have a prolonged response to succinylcholine. The silent variant has 0–10% of normal butyrylcholinesterase activity. About 1 in 100,000 Americans and Europeans is homozygous for silent butyrylcholinesterase, though communities such as the Vysya of India and the Eskimos of Alaska have frequencies as high as 1 out of 24 for homozygous silent butyrylcholinesterase. No single mutation is responsible for the silent variant. The silent butyrylcholinesterase variant includes many types of mutations. Some silent variants have a frameshift mutation, others have an amino acid substitution that destabilizes the enzyme, and others have an insertion.[13]

K-variant butyrylcholinesterase

The "K-variant" is found so frequently that it can be classified as a polymorphism. The K variant (A539T) is found in homozygous form in 1 out of 63 Americans. There are also some so-called quantitative cholinesterase variants of butyrylcholinesterase (K, H, and J type). The K-variant is the most common one, with an allele frequency of 13 %, and it results in a 30% decrease in activity due to the reduction of circulating active enzyme molecules. AG → A base change at position 1615 causes an amino acid alteration Ala539 → Thr.[13,14]

The K-variant causes a 33% reduction in the amount of butyrylcholinesterase circulating in plasma. The catalytic activity per molecule of butyrylcholinesterase is unaffected by the K-variant mutation. Only the quantity of enzymes is reduced. A single amino acid substitution, A539T, is found in the butyrylcholinesterase protein of the K variant. Multiple mutations are common. The atypical mutation is linked to the K-variant mutation, so almost all people who have the atypical mutation also have the K-variant mutation on the same allele.[13]

J-variant butyrylcholinesterase

The J-variant of human serum butyrylcholinesterase (BChE) causes both approximately two-thirds reduction of circulating enzyme molecules and a corresponding decrease in the level of BChE activity present in serum. Since the level of serum BChE activity and the duration of succinylcholine apnea are inversely correlated, this marked decrease in activity makes individuals with the J-variant more susceptible than usual subjects to prolonged apnea from succinylcholine.[14]

DNA amplification by PCR, followed by direct sequencing of the amplified DNA, led to the finding that the J-variant phenotype of human serum BChE was associated with two DNA point mutations in the coding region. One of these was the mutation previously identified with the K-variant phenotype (GCA-*ACA; Ala539--Thr). The other was an adenine-to-thymine transversion at nucleotide 1490, which changed amino acid 497 from glutamic acid to valine (GAA-)GTA; Glu497-0Val). This latter point mutation was named the J-variant mutation (formal name BCHE*497V). The J-variant mutation has not been identified without the K-variant mutation. The J-variant mutation created a RsaI-enzyme RFLP.[15]

C5-variant butyrylcholinesterase

Although most genetic variants of serum butyrylcholinesterase are associated with decreased activity, some rare variants are associated with increased enzyme activity (2 to 3 times normal). These

variants have normal dibucaine and fluoride numbers, and the enhanced activity has been attributed to either an increased number of enzyme molecules or increased activity per active site. One of these is C5-variant BChE. Mass spectrometry has provided strong evidence that the butyrylcholinesterase tetramer has proline-rich fragments within its tetramerization domain, and these proline-rich fragments are derived from multiple proteins, including lamellipodin. The gene for lamellipodin is located on chromosome 2q33, at the site of the unknown protein in the C5 variant.[13-15]

The C5 variant has an extra, slow-moving band of BChE activity on native polyacrylamide gel electrophoresis. This band is about 60 kDa larger than wild-type BChE. Umbilical cord BChE in 100% of newborn babies has a C5-like band. The C5 phenotype has a frequency of about 10% in Caucasians. Individuals phenotyped as C5 has 30% higher plasma BChE activity on average, but activity can range up to 200% higher than the majority of individuals. The C5 phenotype is associated with low body weight and a shorter duration of action of the muscle relaxant succinylcholine.

Potential impact variants of butyrylcholinesterase on human health

Genetic variants of human butyrylcholinesterase were one of the first examples in the new field of pharmacogenetics when it was recognized that abnormal response to the muscle relaxant succinylcholine was due to a mutated enzyme with low binding affinity. Neuromuscular block induced by succinylcholine or mivacurium can be significantly prolonged if the patient has an abnormal genetic variant of butyrylcholinesterase. People who are homozygous for atypical (D70G) or silent butyrylcholinesterase are 100% certain to experience prolonged apnea in response to standard doses of succinylcholine and mivacurium.[10,13]

The K variant of butyrylcholinesterase (BChE- K, 20% incidence) is a long-debated risk factor for Alzheimer's disease. The A539T substitution in BChE-K is located at the C terminus, which is essential both for BChE tetramerization and for its capacity to attenuate β-amyloid (Aβ) fibril formation. This variant has neuroprotective characteristics caused by sustained acetylcholine levels and elevated Alzheimer's disease risk due to inefficient interference with amyloidogenic processes.

2. Conclusion

Genetic variants of human butyrylcholinesterase were one of the first examples in the new field of pharmacogenetics when it was recognized that abnormal response to the muscle relaxant succinylcholine was due to a mutated enzyme with low binding affinity.

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