GSTZ1 Genotype and Cognitive Ability

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The Functions of *GSTZ1*

Glutathione S-transferases (GSTs) catalyse the nucleophilic conjugation of glutathione with a range of electrophilic substances, which represents a major detoxification mechanism in mammals.[1] GST zeta (*GSTZ1*) catalyses the glutathione-dependent isomerisation of maleylacetoacetate to fumarylacetoacetate in the tyrosine catabolic pathway (see *Figure 1*). It also catalyses the oxygenation of dichloroacetic acid (DCA) to glyoxylic acid. DCA does not occur naturally but is present in chlorinated water and is potentially neurotoxic.[2] Genetic polymorphisms in the coding sequence of *GSTZ1* result in significant changes in enzyme function, and it might be expected that this was their major site of action for dopaminergic regulation, but notably they are not implicated in tyrisonaemia, which results from deficiencies of fumarylacetoacetate hydrolase (type 1, most common, affecting the final step of the pathway), tyrosine aminotransferase (type 2, affecting the conversion of tyrosine to p-OH-phenylpyruvic acid) or 4-hydroxyphenylpyruvate dioxygenase (type 3, rare, affecting conversion of p-OH-phenylpyruvic acid to homogentisic acid). Types 2 and 3 are associated with intellectual disability. L-tyrosine is a precursor of dopamine via L-dihydroxyphenylalanine (L-DOPA) and norepinephrine through the action of dopamine β-hydroxylase. Dopamine is also metabolised to the inactive compounds 3,4-dihydroxyphenylacetaldehyde by monoamine oxidase (MAO) and 3-methoxytyramine by catechol-O-methyltransferase (COMT), both ultimately being converted to homovanilic acid. Finally, dopamine can auto-oxidise to 6-hydroxydopamine (6-OHDA), which is neurotoxic, promoting apoptosis.[3,4] 6-OHDA is commonly used to produce an experimental model of Parkinson's disease. By-products of dopamine's auto-oxidation include quinones, free radicals and reactive oxygen species.[5] The glutathione redox cycle helps to regulate the equilibrium between dopamine and its oxidated, neurotoxic product 6-OHDA, e.g. by conjugation of glutathione with dopamine-derived quinones.

> *GSTZ1* is involved in regulating the supply of substrate for dopamine production and in disposal of some of its neurotoxic products.

GSTZ1 is therefore involved in several metabolic pathways, although because there are many GSTs, and other enzymes in the tyrosine catabolic pathway may be more important as rate-limiting steps, its overall contribution is difficult to determine. Of note, however, is that it is involved in regulating the supply of substrate for dopamine production and in the disposal of some of its neurotoxic products.

Dopamine and Cognitive Ability

Dopamine is a major neurotransmitter widely distributed within the brain.[6] Dopaminergic neurotransmission in the pre-frontal cortex (PFC) contributes to individual cognitive differences in animals and humans.[7] Dopamine is also implicated in cognitive deficits seen in schizophrenia and Parkinson's disease. Much attention has focused on a functional variation in the human COMT gene that occurs at a single nucleotide polymorphism (SNP) (*472G>A*), resulting in a valine (Val) to methionine (Met) amino acid substitution (Val158Met). This variant may reduce the thermostability and activity of the enzyme to one-quarter of that encoded by the Val allele,[8] although data from human *post mortem* material suggest that the effect may not be so substantial.[9] Reduced enzyme activity may decrease the degradation and increase the concentration of dopamine.[7] There is an association between Val/Val COMT Val158Met polymorphism and cognitive ability in healthy adults,[10] although data suggest that a shift in the dopamine signalling and PFC function curve occurs with ageing,[11] which is an example of the 'Goldilocks effect' of having just the right amount of dopamine available. Hence, genetic variants may exert different effects on cognition in youth and old age.

GSTZ1 and Ageing

GSTZ1 SNP R42G substitution in humans is associated with both telomere shortening and individual differences in physical biomarkers of ageing, respiratory function and hand-grip strength.[12] Telomere shortening is associated with a broad range of age-related disease, including cognitive disorders.[13–16] In turn, respiratory function and grip strength contribute to the cognitive reserve protective against cognitive decline.[17] The effects of

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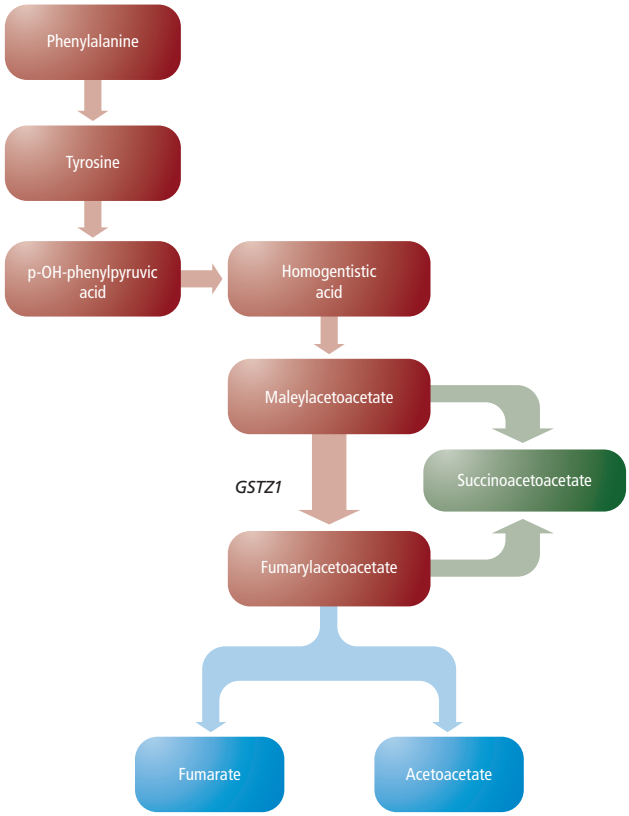
Figure 1: *GSTZ1* Function within the Phenylalanine–Tyrosine Catabolic Pathway



GSTZ1 on telomeres and physical ageing are likely to occur through oxidative stress.[18,19] As yet, there is limited evidence for the effects of oxidative stress genes on normative cognitive ageing.[20,21]

GSTZ1 and Cognitive Studies

The non-linear relationship between dopamine concentrations and cognition forms the background to studies investigating associations between functional *GSTZ1* polymorphisms and cognitive ability. As noted above, beyond its actions as a neurotransmitter within the brain, dopamine and its metabolites are hypothesised to have cytotoxic actions on neurons. Pathways that facilitate the disposal of intracellular dopamine include oxidative deamination by MAO-A, sequestration into synaptic vesicles by vesicular monoamine transporter and metabolism of auto-oxidised products of dopamine by macrophage migration inhibitory factor, as well as GSTs.[22] An alternative hypothesis to explain the 'inverted U' relationship between dopamine levels and cognition is that at high levels dopamine become neurotoxic, especially due to auto-oxidised products.[23]

One recent study administered a broad cognitive test battery to a cohort of 470 community volunteers between 64 and 68 years of age from the 1947 Scottish Mental Survey (SMS 1947) residents in the Aberdeen area with validated childhood IQ data at 11 years of age and whose *GSTZ1-1002* G>A polymorphism was known.[23] There was no significant difference between *GSTZ1* A-carriers and non-carriers in age 11 IQ scores, indicating that the polymorphism has no major effect on cognition in childhood. *GSTZ1* was significantly associated with the underlying cognitive trait at age 64–68 years, with A-carriers having mean scores about 3% lower than non-carriers, with a trend towards performing particularly worse on a test of verbal memory. These findings supported the hypothesis that dopamine disposal pathways influence cognitive ability in older adults. It is plausible that the ageing brain is more vulnerable to increased levels of auto-oxidised products of dopamine than it is in childhood. This would be consistent with the observation that Parkinson's disease incidence increases with age.

GSTZ1 and Parkinson's Disease and Environmental Toxins

Herbicides such as paraquat are implicated as environmental risk factors for Parkinson's disease. Their effect can be attenuated experimentally by protecting oxidative stress pathways.[24] The glutathione redox cycle is affected by paraquat, with a shift towards the oxidised state,[25] accompanied by decreased levels of GSTs. In particular, *GSTP1* is associated with Parkinson's disease in people exposed to pesticides, but no association has been identified for *GSTZ1* so far.[26] The role of *GSTZ1* in the oxygenation of DCA has already been mentioned. However, administration of DCA itself substantially reduces *GSTZ1* activity in animal models.[27] This observation leads to the possibility that, in humans, chronic exposure to chlorinated water will reduce *GSTZ1* activity and consequently increase neurotoxic by-products of dopamine, leading to a greater risk of Parkinson's disease and its concomitant cognitive dysfunction.

GSTZ1 and Normative and Non-normative Cognitive Ageing

Cognitive ageing may be categorised as normative, i.e. non-pathological, and non-normative, e.g. cognitive decline associated with Alzheimer's disease (AD). In fact, even in the presence of moderate AD, some cognitive abilities remain stable and indistinguishable from those in a healthy population.[28] Currently, there is no substantial evidence to indicate that *GSTZ1* is implicated in non-normative cognitive ageing, although there are suggestions that it may predispose to Parkinson's disease. The genetic contribution to human cognitive ability, though thought to be substantial, is yet to be determined adequately.[29] *GSTZ1* is one among many genes that are each likely to contribute only a small amount of the variance in cognitive ability in old age. In view of this genome-wide association, studies may not prove to be very informative. Instead, more hypothesis-driven, pathway-focused investigations are likely to be more fruitful. Such an approach points to future research into genetic polymorphisms of genes that regulate dopamine disposal in addition to COMT and MAO. One candidate is the macrophage migration inhibitory factor gene, which is untested in this regard. Another is the vesicular monoamine transporter protein (VMAT2), which is thought to underpin some of the cognitive deficits observed in bipolar affective disorder.[30]

> This alternative model requires more testing, especially of the effect of other dopamine by-product pathways and of the interaction between such disposal pathway genes and COMT.

Conclusions

Hitherto, the predominant paradigm linking dopamine to cognitive ability has focused on its effects as a neurotransmitter. This paradigm has had

to evolve to account for the non-linear relationship between brain dopamine levels and cognition that changes with age. The observation that *GSTZ1* appears to be associated with cognitive ageing provides support for an alternative paradigm. This is because although *GSTZ1* is involved with tyrosine catabolism, it is unlikely to impact greatly on dopamine concentrations by this mechanism; other factors are more likely to control the availability of tyrosine for conversion to dopamine. In the alternative model an adequate level of dopamine is still considered necessary for neurotransmitter-driven cognitive performance, but as dopamine levels increase so do neurotoxic auto-oxidised by-products of dopamine. The brain, as the underlying substrate, becomes increasingly vulnerable to these auto-oxidised by-products, such as 6-OHDA, as it ages. General redox status, to which *GSTZ1* contributes via the glutathione redox cycle, influences the equilibrium between dopamine and its more neurotoxic metabolites. However, *GSTZ1* is likely to have a more specific role in dopamine by-product disposal. Different isoforms of mainstream enzymes regulating dopamine catabolism, especially COMT, will impact accordingly. Isoforms with high activity will result in lower levels of dopamine and essentially will influence cognitive ability by neurotransmission. Those with low levels of activity will result in high levels of dopamine. This will be beneficial in younger adults in whom the corresponding higher levels of dopamine by-products are less neurotoxic but not in older adults, especially those who have impaired dopamine by-product disposal mechanisms or higher oxidative stress levels. Thus, in older adults, isoforms with intermediate levels of activity are those that confer greatest cognitive benefit.

This alternative model requires more testing, especially of the effect of other dopamine by-product pathways and of the interaction between such disposal pathway genes and COMT. Nevertheless, the model is promising, as it explains current dopamine-related genetic effects parsimoniously and ties in with other disease models of the dopaminergic system. ■

By the Same Author

Oxidadative Stress, Telomere Length and Biomarkers of Physical Aging in a Cohort Aged 79 Years from the 1932 Scottish Mental Survey

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Telomere shortening is a biomarker of cellular senescence and is associated with a wide range of age-related disease. Oxidative stress is also associated with physiological ageing and several age-related diseases. Non-human studies suggest that variants in oxidative stress genes may contribute to both telomere shortening and biological ageing. The authors sought to test whether oxidative stress-related gene polymorphisms contribute to variance in both telomere length and physical biomarkers of ageing in humans. Telomere lengths were calculated for 190 participants (82 men, 108 women) 79 years of age, and associations with 384 SNPs, from 141 oxidative stress genes, identified nine significant SNPS, of which those from five genes (*GSTZ1*, *MSRA*, *NDUFA3*, *NDUFA8*, *VIM*) had robust associations with physical ageing biomarkers, respiratory functio, or grip strength. Replication of associations in a sample of 318 participants (120 males, 198 females) 50 years of age confirmed significant associations for two of the five SNPs (*MSRA* rs4841322, p=0.008; *NDUFA8* rs6822, p=0.048) on telomere length. These data indicate that oxidative stress genes may be involved in pathways that lead to both telomere shortening and physiological ageing in humans. Oxidative stress may explain, at least in part, associations between telomere shortening and physiological ageing. ■

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