Genotype moderates the impact of food additives on hyperactive behavior in children

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1. Abstract

Introduction: The claim of a relationship between artificial food color and additive (AFCs) intake and behavior is highly contentious. We have shown in a previous population-based trial with 3yo children adverse effects of food additives on parentally-rated hyperactive behaviour (Bateman et al, 2004). The possible role of genetic polymorphisms in moderating this adverse effect has not been previously examined. **Methods** A randomised, double blind, placebo-controlled, within subject crossover food challenge was used for 144, 8 to 9 year old children and 153, 3 year old children. Following baseline assessment children were placed on a diet eliminating food additives and a benzoate preservative for 6 weeks during which time they were challenged for weekly periods with either a placebo mix or a drink containing sodium benzoate (45mg daily) and one of two mixes of AFCs.: **Results:** The T939C and Thr105Ile polymorphisms of the histamine N-methyltransferase gene (HNMT) moderated the adverse effect s of AFCs but the polymorphisms in catecholamine genes COMT Val108Met and ADRA2A C1291G did not. These findings point to a possible role for histamine in mediating the effects of food additives and help to explain why there has been inconsistency between previous studies. **Conclusions:** Genes influencing a range of neurotransmitter systems and their interplay with environmental factors, such as diet, need to be examined to understand genetic influences on hyperactivity.

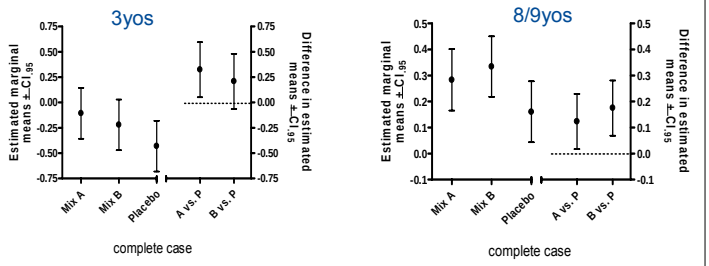
2. Background

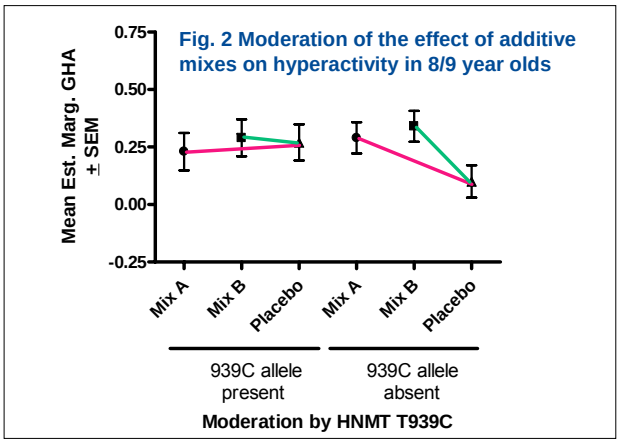
Hyperactivity in children is characterized by inattention, impulsivity and overactivity. In addition, **Artificial food colors (AFCs)** and other food additives have an adverse effect on children with ADHD.[1] There is less clear evidence for the adverse effect of AFCs on behavior in children in the general population. A previous study using double blind controlled challenges conducted by us on the Isle of Wight has suggested an adverse effect of AFCs on the behaviour of 3 year old children.[2] We have shown that mixtures of some food colours and a sodium benzoate preservative can increase the level of hyperactivity in children from the general population.[3] These results came from a double-blind placebo controlled cross-over trial of two additive mixes administered in doses equivalent to the daily average intake for a child population :

Mix A – sunset yellow (E110), carmoisine (E122), tartrazine (E102), ponceau 4R(E124) and sodium benzoate (E211).
Mix B – sunset yellow (E110), carmoisine (E122), quinoline yellow (E104), allura red AC(E129)) and sodium benzoate(E211).

Figure 1 illustrates the elevation of hyperactivity levels for 3yos (n=153) and for 8/9yos (n= 144).

Fig.1 Effect of additive mixes on hyperactivity





3. Genetic moderation of the effect of food additives

DNA was extracted from buccal cells in these children and genotyped for two histamine N-mtheyltransferse single neucleotide polymorphisms (SNPs) in the histamine N-methyltranferase gene, Thr105Ile (rs1801105) and T939C (rs1050891), for one SNP in the dopamine gene, catechol-o-methyltransferase (COMT Val108Met, rs4680), and one SNP in the adrenergic neurotransmitter system, adrenergic receptor alpha 2A (ADRA2A C1291G, rs1800544).

The key question :
do these SNPs show an interaction with the effect of food challenge.

Fig. 2 shows that for 8/9yo children a moderating effect of the 939C present genotype was found which significantly reduced the adverse effect of Mix A (p=.021) **(difference in pink)** and of Mix B (p=.026) **(difference in green)**. A similar effect for 105Ile present genotype for Mix B with 3yos. fell just short of significance (p=.061). The 105Ile present genotype moderated the effect of Mix A in 3 yos. (p=.041) but not for 8/9-yos. The COMT Val108Met and ADRA2A C1291G polymorphisms did not show any moderating effect at either age 3 or 8/9-years of age for either Mix.

4. Conclusions

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- there is a link between histamine and hyperactivity
- HNMT polymorphisms impair histamine clearance4
- H3 receptors in the brain provide a potential mechanism for the effect6
- is this why food allergy/intolerance is suggested to be a cause of hyperactivity?
- current focus on dopamine in studies of ADHD needs to be extended.
- polymorphisms in the HNMT gene moderate behavioural responses to AFCs
- an AFC challenge causes histamine release5
- many environmental factors will increase histamine release, e.g. infections and food.
- doe this explain the effects of infections in aggravating behavior?
- such gene x environment interactions may contribute to effects on ADHD
- this proposed mechanism clearly indicates a potential target for therapeutic intervention in ADHD focused on the H3 receptor.

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