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ADHD impacted by sulfotransferase (SULT1A) inhibition from artificial food colors and plant-based foods

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HIGHLIGHTS

• SULT1A inhibition in the gut can increase plasma tyrosine and brain dopamine.
• Artificial colors are SULT1A inhibitors, as are many natural polyphenols in foods.
• Prior ADHD trials were compromised by including multiple SULT1A inhibitors.
• Prior trials show evidence of SULT1A inhibition causing ADHD symptoms.
• Prior trials support an inverted-U ADHD response to SULT1A inhibition.

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ABSTRACT

Background: Five recent reviews have analyzed trials on the association between artificial food colors and ADHD; the 50 underlying studies and the reviews in aggregate were inconclusive. Recent work has shown human *in vivo* SULT1A inhibition leading to incremental catecholamines, and an inverted-U relationship between brain catecholamines and proper functioning of the prefrontal cortex where ADHD behavior can arise.
Method: This study re-examined the same underlying trials for evidence that SULT1A inhibitors were in the placebos and other inactive foods, that these “inactive” materials were symptomatic, and that ADHD symptoms exhibited an inverted-U response to SULT1A inhibition.
Results: Nearly all the underlying diets, and many placebos and delivery vehicles, were found to contain SULT1A inhibitors. Eight publications provided evidence of ADHD symptoms caused by the “inactive” materials containing SULT1A inhibitors. Ten studies showed additional SULT1A inhibitors reducing the symptoms of some subjects.
Conclusion: SULT1A inhibitors in foods, including natural substances and artificial food colors, have a role in ADHD that can both worsen or improve symptoms. Mechanistically, SULT1A enzymes normally deactivate catecholamines, especially dopamine formed in the intestines; SULT1A inhibition can influence brain catecholamines through the intermediary of plasma tyrosine levels, which are influenced by dopamine inhibition of intestinal tyrosine hydroxylase. Biochemical measurements focused on SULT1A activity and plasma tyrosine concentrations are proposed for future work.

1. Introduction

ADHD is thought to impact a significant fraction of school-age children, causing inappropriate behavior and impacting the childrens' ability to learn. In 1974, Feingold proposed that removal of artificial food colors from a child's diet reduced or eliminated the symptoms. The proposals were, and have remained, controversial. Anecdotal evidence from some parents is supportive of the theory, but clinical work has been unclear in spite of many studies.

Several reviews [1–5] of ADHD clinical studies focused on artificial food colors have been released since 2010. In keeping with the equivocal findings in many of the underlying clinical studies, the review articles do not reach consistent conclusions. Key review findings, in chronological order of publication, include: “Overall, the available information … does not support a causal relationship of … artificial food colors/preservatives in particular with ADHD or other problem behaviors in children.” [1]. “Artificial food colors (AFCs) have not been established as the main cause of attention-deficit hyperactivity disorder (ADHD), but accumulated evidence suggests that a subgroup shows significant symptom improvement when consuming an AFC-free diet and reacts with ADHD-type symptoms on challenge with AFCs.” [2]; “We believe that the balance of existing evidence neither refutes nor

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supports the links between AFCs and ADHD …" [3]; "A restriction diet benefits some children with ADHD. Effects of food colors were notable … but susceptible to publication bias or were derived from small, nongeneralizable samples." [4]; "Recent data suggest a small but significant deleterious effect of AFCs on children's behavior that is not confined to those with diagnosable ADHD" [5].

A primary difficulty in connecting food colorings and ADHD has been the lack of a mechanistic bridge between the two. There is a growing body of literature suggesting dopamine (DA) and norepinephrine (NE) involvement in ADHD; for example, Arnsten [6] has demonstrated that either too little or too much DA or NE lead to dysfunction in the prefrontal cortex, where symptoms of ADHD are thought to arise. These phenomena will be referred to below as Low-Catecholamine Hyperactivity (LCH) and High-Catecholamine Hyperactivity (HCH), as compared to Neutral Catecholamine Non-Hyperactivity (NCNH). With DA and NE as key links in the ADHD chain, we should consider how food colors could affect DA or NE levels.

The body synthesizes DA from L-dopa, which is in turn produced from tyrosine; tyrosine is ingested as part of our protein intake, or produced by conversion of phenylalanine that is also part of protein intake. DA can be converted to NE and then epinephrine (E). All three catecholamines (DA, NE, and E) can be deactivated by three enzyme groups; monoamine oxidases A & B, catechol-O-methyltransferase (COMT), and the sulfotransferases SULT1A1 and especially SULT1A3. 97% of DA and 73% of NE in plasma circulate in the inactive sulfate form resulting from SULT1A deactivation, illustrating the importance of the sulfotransferases [7].

The SULT1A1 and SULT1A3 enzymes are inhibited *in vitro* by a wide range of naturally-occurring polyphenols from plants [8–13]. There is also *in vitro* evidence that artificial food colors inhibit SULT1A1 and SULT1A3 enzymes [8,14]. A recent article [15] gathered results from 19 published studies suggestive of human *in vivo* SULT1A inhibition after ingestion of natural polyphenols from plant-based foods, evidenced through direct measurement of catecholamines or through symptoms strongly indicative of excess catecholamines.

Details of the proposed mechanism follows in the Discussion section. In summary, SULT1A inhibition in the gut can lead to increased tyrosine in the brain, which sources incremental DA and NE in the brain. For HCH subjects, it is reasonable to expect that this can exacerbate ADHD symptoms given the results from Arnsten [6]. Similarly, for LCH subjects, we could expect that SULT1A inhibition would reduce their symptoms by raising DA and NE to more-normal levels. For NCNH children, SULT1A inhibition could be symptomatic if it pushes them into the HCH range or non-symptomatic if they remain within normal DA and NE ranges. The implied ambiguity, whereby incremental SULT1A inhibition can increase, decrease, or have no apparent effect on ADHD symptoms, is problematic. It means that even well-constructed experiments will yield variable changes in behavior depending on the then-current state of the subject's brain catecholamine concentrations, the amount of tyrosine reaching the intestines, and intestinal SULT1A activity. The intent of this work is to look for evidence of these types of ambiguities in the prior clinical studies, and to propose a new experimental methodology based on the hypothesized underlying biochemistry.

2. Methods

Five reviews published in 2010 or later were identified that examined clinical studies of artificial food colors and ADHD [1–5]. A total of 50 clinical studies [16–65] were addressed in at least one of those reviews; on average, each study was cited in 2.5 reviews. With the exceptions stated below, these studies were re-analyzed in light of the above discussion, focusing on three issues;

1) Food colors likely represent only a portion of the ADHD-active class of SULT1A inhibitors. Did the experimental protocol prevent confounding influences from other SULT1A inhibitors that could interfere with the results? In particular, did the "inactive" placebos, delivery vehicles, or baseline diets include SULT1A inhibitors?
2) Was there any evidence that the placebos or delivery vehicles in fact caused symptoms of ADHD?
3) Was there any evidence that some subjects had their ADHD symptoms reduced after ingesting high doses of colorings?

Two studies mentioned in the review articles are not used in this work. The study by Fitzsimon et al. [60] reports on trials where acetylsalicylic acid was the active chemical and ascorbic acid the placebo; while the Feingold diet was designed to eliminate salicylates, this study is not directly relevant to the effects of artificial colors on ADHD. One cited study [51] is a review article that does not present new experimental data.

Also, it should be noted that three studies by Conners [62–64] mentioned in the review of Kleinman et al. [3] present the same results as reported by Conners [24] that was used in the Sobotka review [1]; all four studies are mentioned in this analysis because the accompanying commentaries provide different details.

No informed consent or IRB approval was necessary for this re-analysis of existing published material.

3. Results

3.1. Presence of SULT1A inhibitors in the "inactive" components of the studies

Plant-based foods including fruits, vegetables, spices, and drinks from fruits and vegetables whether fermented or not, contain a wide variety of polyphenols, many of which have been demonstrated to be SULT1A inhibitors. A website focused on the polyphenol contents of such foods is available [66]. Certain foods mentioned below, including chocolate (catechin, epicatechin), orange (hesperitin), apple (epicatechin, quercetin), cranberry (quercetins), and broccoli (chlorogenic acid) contain confirmed SULT1A inhibitors.

Seven of the studies used an oligoantigenic baseline diet. In one study [16], this is described as "consisting typically of two meats (e.g., lamb and chicken), two carbohydrate sources (e.g., potatoes and rice), two fruits (e.g., banana and apple), vegetable (e.g., any brassica), water, calcium, and vitamins." The diet was adjusted to suit the families, and avoid foods of which the families were suspicious. Egger et al. [17] used virtually the same words, changing the apple to pear and expanding the list of vegetables to cabbage, sprouts, cauliflower, broccoli, cucumber, celery, and carrots. In 1993, Carter et al. [18] again used the same description but with vegetables described as "a range of root and green vegetables," while adding sunflower oil and milk-free margarine. Uhlig et al. [19] used the diet from Egger et al. [17]. In 1997, Schmidt et al. [20] used essentially the same foods, substituting turkey for the chicken. Two recent studies [52,61] used a diet similar to that of Carter et al. [18], supplemented in some cases with potatoes, fruits, and wheat.

Twenty-six of the studies [21–39,54,55,59,62–65] describe their baseline diet as Feingold (also known as KP) or modified Feingold. Also, Breakey et al. [50] used a Feingold diet but allowed additional vegetables, and Loblay and Swain [53] used a low-salicylate diet that is probably Feingold type. All eliminated artificial colors and flavors. The primary difference between Feingold and modified Feingold is the inclusion of fruits that Feingold identified as sources of natural salicylates. It is not always clear whether diets referred to as "Feingold" nevertheless allowed access to salicylate-containing fruits. Regardless, even a strict Feingold diet allows access to chocolate, grapefruit, pineapple, pear, guava, vanilla (natural only), homemade mustard, all spices except cloves, and vegetables except tomatoes and cucumbers [67].

Another group of studies [40–48] use diets free of artificial colors, and sometimes artificial preservatives, similar to modified Feingold but not identified as such.