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Toxicological effects of red wine, orange juice, and other dietary SULT1A inhibitors via excess catecholamines

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ABSTRACT

SULT1A enzymes protect humans from catecholamines, but natural substances in many foods have been found to inhibit these enzymes *in vitro*. Given the hormonal roles of catecholamines, any *in vivo* SULT1A inhibition could have serious consequences. This paper uses a re-analysis of published data to confirm that SULT1A inhibitors have effect *in vivo* in at least some patients. Nineteen studies are cited that show ingestion of SULT1A inhibitors leading to catecholamine increases, blood pressure changes, migraine headaches, or atrial fibrillation. SULT1A inhibition does not create the catecholamines, but prevents normal catecholamine deactivation. Susceptible patients probably have lower-activity SULT1A alleles. The paper discusses new hypotheses that SULT1A inhibition can cause "holiday heart" arrhythmias and type 2 diabetes in susceptible patients. Subgroup analysis based on SULT1A alleles, and addition of a catecholamine source, should improve the consistency of results from tests of SULT1A inhibitors. SULT1A inhibition may be a key contributor to cheese-induced migraines (via annatto), false positives in metanephrine testing, and the cardiovascular impacts of recreational alcohols.

1. Introduction

The cytosolic sulfotransferases (SULTs) catalyze the sulfonation of endobiotics and exobiotics (Strott, 2002). Five enzyme families are known in mammals, which target different substrates for sulfonation. SULT1 focuses on phenolics and catecholamines (SULT1A), thyroid hormones (SULT1B), xenobiotics (SULT1C), and estrogenic steroids (SULT1E). SULT2 enzymes sulfonate neutral steroids and sterols, while SULT3 catalyzes the formation of sulfamates. SULT4 and SULT5 have not been fully characterized.

The SULT1A enzymes are critical to protecting humans from xenobiotics and ingested catecholamine precursors, sometimes called the "gut-blood barrier" (Eisenhofer et al., 1999). Planar phenolics are preferentially sulfonated by SULT1A1. More-complicated molecules such as tyrosine and dopamine are preferentially sulfonated by SULT1A3 and its duplicate SULT1A4 (throughout the remainder of this paper, SULT1A3 will be used to represent both SULT1A3 and SULT1A4, except where noted). The role and expression pattern of SULT1A2 is not well understood. Sulfonation usually makes a molecule more hydrophilic, facilitating elimination in the urine (Hempel et al., 2005). There are several known non-synonymous polymorphisms that significantly affect SULT1A activities. Therefore, an individual's response to SULT1A inhibitors will depend both on the inhibitors ingested and the individual's version of the SULT1A genes (Coughtrie and Johnston, 2001). The implications of various polymorphisms for individuals and ethnic groups are discussed in Section 4.

Approximately 45% of the dopamine formed in humans is created in the intestine (Eisenhofer et al., 1997). Most of this is normally immediately inactivated by SULT1A3, such that ca. 97% of the dopamine in blood plasma is in the inactive sulfonated form (Strott, 2002). Unsulfonated, or free, dopamine is the precursor to the other catecholamines norepinephrine and epinephrine. These also circulate primarily in inactive sulfonated forms (norepinephrine ca. 73% sulfonated, epinephrine ca. 84% sulfonated).

Besides acting as neurotransmitters, the catecholamines have significant hormonal functions, working to ready the fight-or-flight response. Pheochromocytoma is a relatively rare condition where adrenal tumors produce excess catecholamines (Hughes et al., 2010). Other mechanisms that reduce the fraction of sulfonated catecholamines in favor of free catecholamines would be expected to have similar effects.

The catecholamines are used medicinally.[1] Side effects for dopamine and epinephrine include heart palpitations, headaches, dizziness, and nausea. Norepinephrine side effects include a slowed heart rate, headaches, and high blood pressure. Pheochromocytoma typically presents similar symptoms, including high blood pressure, headaches, sweating, and heart palpitations.

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[1] Dopamine, http://www.medicinenet.com/dopamine-injection/article.htm, Epinephrine http://www.netdoctor.co.uk/medicines/100000940.html, Norepinephrine http://www.netdoctor.co.uk/medicines/100001496.html.

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Several researchers have studied the *in vitro* inhibition of SULT1A enzymes by food constituents and additives. For example, Nishimuta et al. (2007) show that orange juice, grapefruit juice, and various teas significantly inhibit both SULT1A1 and SULT1A3. Table 1 summarizes inhibition extents and common sources of some known inhibitors.

The present study uses previously reported but unexplained evidence from human trials to demonstrate that SULT1A inhibition also occurs *in vivo* in susceptible individuals. The resulting increased concentrations of circulating free catecholamines are shown to have significant health impacts, with focus on three common symptoms: blood pressure, headaches (specifically migraine headaches), and palpitations (specifically atrial fibrillation).

2. Methods

The experimental data used in this analysis comes from existing literature sources where ingestion of SULT1A inhibitors was followed by measurement of catecholamines or common side effects of catecholamines. Studies were excluded based on the following criteria.

Some blood pressure studies of chocolates compare dark chocolate to a white chocolate control (e.g., Taubert et al., 2007; Grassi et al., 2008). These were excluded because dark chocolate contains theobromine, which is known to affect blood pressure (van den Bogaard et al., 2010), while white chocolate does not. Similarly, studies using *citrus aurantium* (bitter orange) were eliminated because it contains significant amounts of synephrine, which also increases blood pressure (Bui et al., 2006).

Three double-blind studies looking at chocolate and migraines (Moffett et al., 1974; Gibb et al., 1991; Marcus et al., 1997) are inappropriate for testing a SULT1A-inhibition mechanism. Both chocolate and placebo samples in the studies included peppermint, and in the latter two studies both samples included carob powder. Peppermint (Neveu et al., 2010) and carob (Rakib et al., 2010) have very high phenolic concentrations and are likely SULT1A inhibitors.

Studies of habitual coffee drinkers (e.g., Smits et al., 1985; van Dusseldorp et al., 1989) were excluded, as these are primarily caffeine trials rather than SULT1A inhibitor trials.

Only human *in vivo* studies are included. Further *in vitro* evidence beyond that shown in Table 1 is not relevant to this study. Non-primate mammals do not have a SULT1A3 ortholog (Riches et al., 2009); given the potential importance of SULT1A3 inhibition to the mechanism, studies in mammals other than primates were excluded. No non-human primate studies relevant to SULT1A inhibition were discovered.

3. Evidence of catecholamine effect

Section 3.1 discusses studies that provide direct measurements of catecholamine increases after SULT1A-inhibitor ingestion. Linkages between SULT1A inhibitors and three common effects of catecholamines (blood pressure changes, migraine headaches, and atrial fibrillation) are addressed in Sections 3.2–3.4.

Table 1
SULT1A inhibitors, extent of inhibition, and common sources.

Substance	SULT1A1 inhibition	SULT1A3 inhibition	Common sources
Quercetin[a]	Complete	Partial	Chocolate, onion, blueberry
Hesperetin[b]	Extr potent	Extr potent	Lime, orange, lemon
Vanillin[c]		Strong	Chocolates, ice cream
Curcumin[b]	Effective	Effective	Turmeric
Resveratrol[d]	65%	75%	Muscadine wines, lingonberry
Quinic acid[d]		75%	Coffee beans
Caffeic acid[e]	8%	3%	Coffee, sunflower seed
Chlorogenic acid[e]	4%	5%	Coffee, blueberry, plum
Protocatechuic acid[e]	21%	15%	Chicory
Sinapic acid[e]	9%	24%	Olives, cauliflower
Syringic acid[e]	22%	15%	Walnuts, dates, olives
Vanillic acid[e]	29%	18%	Olives
Naringin[a]		Partial	Grapefruit
Nobiletin[a]	Complete		Orange
Tangeretin[a]	Complete		Orange
Brandy extract, not ethanol[f]	66%	16%	Brandy
Red wine extract, not ethanol[f]	99%	12%	Red wine
Sherry extract, not ethanol[f]	80%	9%	Sherry
Whiskey extract, not ethanol[f]	56%	5%	Whiskey
White wine extract, not ethanol[f]	72%	5%	White wine
Vodka extract, not ethanol[f]	34%	4%	Vodka
Gin extract, not ethanol[f]	20%	3%	Gin
+catechin[c,g]	100%	Strong	Cocoa, chocolate, red wine
Epicatechin gallate[a,d]	Alm Compl	Alm Compl	Tea, grapes, peppermint
Epigallocatechin gallate[a,d]	Alm Compl	Alm Compl	Tea, pecans
Gallocatechin gallate[d]	100%	100%	Tea
Trigonelline[d]	5%	80%	Coffee beans
Theaflavin fractions of black tea[a]	Complete		Tea
Thearubigin fractions of black tea[a]	Complete	Strong	Tea
Octyl gallate[c]		Strong	Antioxidant E311
Tartrazine[c]		Strong	FD&C Yellow 5
Eriodictyol[b]	Extr potent	Extr potent	Lemon
Carmoisine[g]	100%		Synthetic colorant E122
Cyanidin 3-rutinoside[g]	100%		Blackcurrant, cherries, olives
Salicylic acid[h]	50%		Fennel, cranberry, cinnamon

Extr Potent – Extremely potent, Alm Compl – Almost complete.
[a] Nishimuta et al. (2007).
[b] Coleman (2010).
[c] Bamforth et al. (1993).
[d] Coughtrie and Johnston (2001).
[e] Yeh and Yen (2003).
[f] Littlewood et al. (1985).
[g] Gibb et al. (1987).
[h] Harris et al. (1998).

3.1. SULT1A inhibitors can increase plasma catecholamines

Section 3.1.1 discusses the standard warnings about foods to be avoided before catecholamine/metanephrine testing. Sections 3.1.2–3.1.6 provide reports of measured *in vivo* catecholamine responses to ingested SULT1A inhibitors; reported catecholamines in Section 3.1.4 were based on urine testing, while the other studies measured plasma concentrations directly. Sections 3.1.2–3.1.5 reflect responses in healthy volunteers. The statistical significance of the results, where reported, is shown. None of these results were explained by conventional mechanisms.

3.1.1. Patient preparation for catecholamine testing

The American Association for Clinical Chemistry include the following warning in a website[2] about urine testing for the catecholamine metabolites metanephrine and normetanephrine: "Foods such as coffee (including decaf), tea, chocolate, vanilla, bananas, oranges and other citrus fruits should be avoided for several days prior to the test and during collection." Clinical experience has demonstrated that these foods interfere with the test by increasing catecholamine metabolite levels. This is evidence of an *in vivo* effect where SULT1A inhibitors lead to increased catecholamines.

3.1.2. Dopamine increases vary by type of alcohol

Spaak et al. (2008) describe experiments where 13 healthy volunteers were given water, ethanol, or red wine in three separate sessions. Subjects were monitored for a number of factors including blood pressure, heart rate, and plasma catecholamine concentrations. In both the water and ethanol trials, plasma free dopamine remained in the 10–35 pmol/L range. However, one glass of red wine raised plasma dopamine to 470 ± 127 pmol/L, while two glasses raised it to 840 ± 248 pmol/L. Epinephrine and norepinephrine concentrations, and blood pressure, did not show any statistically significant changes from red wine or ethanol. Plasma concentrations of resveratrol and catechin rose significantly after drinking the wine. Neither the ethanol nor water contained resveratrol or catechin.

Boyer et al. (2004) report on forty healthy volunteers given champagne, still white wine, and sparkling water. Plasma dopamine concentrations were measured after drinking 100 ml of the beverages. Dopamine levels were significantly higher after champagne than after sparkling water ($p = 0.0183$). Dopamine was also somewhat higher after champagne than after still white wine ($p = 0.0693$). Sparkling water did not effect plasma dopamine concentrations, so CO_2 was discarded as a potential cause. The authors proposed that the dopamine difference after champagne versus white wine might have been due to the different fermentation processes or gastric distension. An alternative explanation is that most champagne, while looking like white wine, is made from a nearly-equal mix of white and red grapes.[3] Red wine is a more-effective SULT1A inhibitor than white wine (see Table 1); the red wine grapes probably in the champagne could explain the dopamine difference.

3.1.3. Norepinephrine and epinephrine increase from lingonberry juice

Heikkonen et al. (1991) performed studies on eight healthy men looking at the effects of alcohol and exercise. In the control test, the subjects were given lingonberry juice diluted with water over the course of two hours. Blood samples before and after the drinking period showed a 2-fold ($p < 0.05$) increase in norepinephrine and a significant ($p < 0.01$) increase in epinephrine. The phenol-explorer database (Neveu et al., 2010) confirms that lingonberry contains resveratrol and caffeic acid.

3.1.4. Norepinephrine increase from green tea extract

Ten healthy men were given green tea extract containing epigallocatechin gallate and caffeine in a double-blind design focused on energy expenditures (Dulloo et al., 1999). Urinary norepinephrine increased from 160 ± 14 nmol per 24 h with the placebo, and 187 ± 29 with caffeine only, to 219 ± 27 with the tea extract. Norepinephrine after tea extract was significantly different than after placebo ($p < 0.05$), while the result after caffeine-only was not. The authors also point out that dopamine "tended to be highest during treatment with the green tea extract," but not sufficiently to reach statistical significance. Epinephrine was also measured, but did not increase.

3.1.5. Epinephrine increase from decaffeinated coffee

In Graham et al. (1998), nine healthy volunteers were given regular coffee, decaffeinated coffee, or water, plus placebo or caffeine capsules, followed by exercise. Higher plasma epinephrine concentrations were seen after decaffeinated coffee than after placebo plus water, although both results were lower than after ingestion of caffeine or regular coffee. The statistical significance of the decaffeinated coffee vs. placebo result was not stated. Plasma free norepinephrine concentrations rose in all cases during the exercise period, but with no significant differences between the placebo and other regimes.

3.1.6. Norepinephrine increase from orange juice

Kuchel et al. (1982) documented a pheochromocytoma patient who made detailed observations of foods that triggered hypertensive crises. Orange juice, red wine, mustard, and vinegar are among the identified triggers, all of which contain SULT1A inhibitors (Neveu et al., 2010). A challenge was carried out in the hospital prior to surgery to remove the adrenal tumors. Within minutes of drinking 500 mL of orange juice, the patient's plasma free norepinephrine increased from 0.36 to over 2.6 ng/mL. Blood pressure also increased, as detailed in Section 3.2.4. There is no statistical significance associated with this single observation; however, the final concentration is over the 2.5 ng/mL usually required to produce hemodynamic and metabolic changes during norepinephrine infusion (Fitzgerald, 2007). Kuchel believed that synephrine was the active agent, but common orange juice (from *Citrus sinensis*) contains little or no synephrine. Synephrine is found in significant quantities in Seville orange (*Citrus aurantium*) and Mandarin orange (*Citrus unshiu*), which may explain the error.

Results from a pheochromocytoma patient are probably not applicable to healthy patients. This example is however useful in illustrating the interaction between SULT1A inhibition and a catecholamine source. This is addressed in Section 4.

3.2. SULT1A inhibitors can change blood pressure

In healthy patients, catecholamines have varied effects on blood pressure. For example, in Fitzgerald (2007), both systolic and diastolic blood pressure is said to increase above norepinephrine concentrations of 2500 pg/mL. However, systolic pressure increases while diastolic decreases above epinephrine concentrations of 500 pg/mL. Dopamine acts as a vasodilator at above-normal concentrations, but as a vasoconstrictor at extremely high concentrations. The following studies show changing blood pressure in response to ingestion of SULT1A inhibitors. Whether blood pressure moves up or down, the notable feature of the reports is that blood pressure is affected at all. Sections 3.2.1 and 3.2.4 reflect responses in healthy volunteers.

[2] http://labtestsonline.org/understanding/analytes/urine-metanephrine/tab/sample accessed October 17, 2011.

[3] http://www.champagneinfo.net/Productie/DeDruiven/tabid/176/Default.aspx accessed November 29, 2011.

3.2.1. Blood pressure increase from decaffeinated coffee

Corti et al. (2002) show a 12 ± 3 mm Hg rise in systolic blood pressure ($P = 0.033$) in nine non-habitual coffee drinkers after drinking decaffeinated coffee; blood samples confirmed no increase in plasma caffeine. The same subjects showed a 12.6 ± 1.6 mm Hg rise in systolic pressure ($P = 0.001$) after drinking regular coffee. Habitual coffee drinkers showed a 2.3 ± 1.6 mm Hg rise in systolic pressure ($P = 0.227$) after drinking regular coffee. Diastolic pressure was unchanged after non-habitual drinkers had decaffeinated coffee. After regular coffee, diastolic pressure was up significantly in non-habitual drinkers (7.1 ± 1.6 mm Hg, $p = 0012$), but not in habitual drinkers (0.7 ± 3.4 mm Hg). The authors concluded, "... ingredients other than caffeine must be responsible for cardiovascular activation."

3.2.2. Blood pressure decrease from quercetin

Edwards et al. (2007) show reductions of 7 ± 2 mm Hg systolic pressure and 5 ± 2 mm Hg diastolic pressure in hypertensive adults (both results $P < 0.01$). This was a randomized, double-blind, placebo-controlled, crossover study. Nineteen prehypertension and 22 stage 1 hypertensive male and female patients were given 730 mg quercetin/d for four weeks. The prehypertensive volunteers showed no changes in blood pressure from the quercetin regime.

3.2.3. Blood pressure decrease from mixed berries containing polyphenols

Erlund et al. (2008) show reductions of 7.3 mm Hg systolic pressure ($P = 0.024$) in their highest-baseline-BP subgroup. Patients consumed mixed berries in an 8-week study. Diastolic pressures, and systolic pressures in the two lower-baseline-BP subgroups, did not change significantly. The study used 72 middle-aged Finns with cardiovascular risk factors in a single-blind, randomized, placebo-controlled design.

The berries yielded a mean daily intake of 837 mg of total polyphenols, including anthocyanins, procyanidins, phenolic acids, ellagitanins, and flavonols. Blood samples showed increased concentrations of the SULT1A inhibitors quercetin, caffeic acid, protocatechuic acid, and vanillic acid in the berry group after the 8-week period.

3.2.4. Blood pressure changes from hesperidin and orange juice

Morand et al. (2010) show reductions in diastolic pressure of 5.3 ± 2.0 mm Hg from hesperidin and 4.5 ± 2.0 mm Hg from orange juice ($P < 0.05$). The subjects were 24 healthy but overweight men in a randomized, placebo-controlled, crossover study. Subjects were given 500 mL orange juice naturally containing 292 mg hesperidin, or a control drink with an equivalent amount of added hesperidin, for 4 weeks. Systolic pressures did not change significantly.

For Kuchel's pheochromocytoma patient discussed in Section 3.1.6, the orange juice triggered a blood pressure increase from 140/85 to 270/112. This case is also discussed in Section 4.

3.3. SULT1A inhibitors can trigger migraine headaches

It is estimated that approximately 15–18% of women and 6–7% of men will have experienced migraines in the past year (Davidoff, 2002). Lifetime prevalences are estimated at 12–33% of women and 4–22% of men. Between 10% and 50% of migraine patients believe that at least some of their migraines are triggered by food.

3.3.1. Migraines from red wine but not from vodka

In a blind test, 9 of 11 patients given red wine developed a migraine headache that day, while none of eight patients given vodka developed a migraine. Littlewood et al. (1988) tested 19 patients who stated that their migraine headaches were typically provoked by red wine but not vodka. The wine had a low tyramine content of 2 mg/L, eliminating that as a potential cause of the headaches. The authors concluded, "...red wine contains a migraine-provoking agent that is neither alcohol nor tyramine." As shown in Table 1, vodka inhibits SULT1A roughly 1/3 as much as red wine. Section 3.1.2 indicates increased levels of dopamine after SULT1A inhibition; dopamine is believed to be a key contributor to migraine headache (Charbit et al., 2010). Vodka, in the amounts tested in Littlewood's study, apparently does not yield sufficient inhibition to trigger a migraine.

3.3.2. Migraines from chocolate, cheese, citrus, coffee, and alcohols

Peatfield et al. (1984) show that 19% of 490 migraine patients reported chocolate as a migraine precipitant, 18% cheese, 11% citrus fruit, and 7% coffee. Twenty nine percent blamed alcohols especially red wine. In a study of 577 patients attending a migraine clinic, Peatfield (1995) found that "about one fifth of migraine patients report sensitivity to cheese and chocolate, ..., and nearly always to citrus fruit as well." Eleven percent indicated that headaches could be induced by red wine but not white wine or clear spirits. Sensitivity to all forms of alcohol was reported by 17%.

Fukui et al. (2008) interviewed 200 migraine patients in Brazil (81% women), using a predetermined list of potential trigger factors. Patients were allowed to identify multiple triggers. 34% identified alcohol as a trigger, 20% chocolate, 19% red wine, 14% coffee, and 10% white wine. All other listed dietary items (sausage, salami, monosodium glutamate, cheese, milk, aspartame, soft drink, citric fruits, ice cream, and nuts) were chosen by less than 10% of interviewees.

Chocolate, citrus, coffee, and many alcohols, accounting for a significant fraction of the reported migraines, contain SULT1A inhibitors as shown in Table 1. These substances grow on plants or are extracted from plants, and could be expected to be SULT1A inhibitors. Ice cream typically includes chocolate, fruit, or plant-based flavorings such as vanillin or mint, and many sodas include natural flavorings from plants. Cheese is the apparent exception. It is commonly believed that the active migraine-triggering ingredient in cheese is tyramines (Davidoff, 2002). With the exception of hypertensive crises in patients taking MAO-inhibitors, the evidence for tyramine impacts is mixed. Other tyramine-rich foods are not usually seen as migraine triggers, and tests of tyramine itself have not consistently triggered migraines. However, many cheeses include annatto, a natural food coloring from the *Bixa orellana* tree.[4] Annatto has been found to contain phenolics including hypolaetin and a caffeoyl acid derivative (Chisté et al., 2011), and is most likely a SULT1A inhibitor.

3.3.3. Migraines from alcohols during stress

In a study of 307 subjects who suffered from migraines without aura (Nicolodi and Sicuteri, 1999), low doses of alcohol were associated with significantly lower frequency of migraine ($p > .0001$). They also found that alcohol consumption during stressful periods led to a significantly higher frequency of migraines (e.g., $p > 0.002$ for red wine). The linkage between inhibitor consumption and stress will be discussed in Section 4.

3.3.4. Migraines from vanillin

A mother and her two children were reported to suffer migraines after regular consumption of foods containing vanillin (Saint Denis et al., 1996). There was no controlled testing, but

[4] http://www.inchem.org/documents/jecfa/jecmono/v52je03.htm accessed December 3, 2011.

the symptoms stopped after an elimination diet and resumed upon reintroduction.

Vanillin is an important SULT1A inhibitor because of its widespread occurrence in foods known to trigger migraines. Alcohols aged in oak contain vanillin; lignin degradation forms the vanillin, which is extracted into the alcohol (Puech, 1981). Many commercially-available chocolates include vanillin (as natural vanilla extract or artificially produced vanillin). Coffee is popularly sold in French Vanilla flavor.

3.4. SULT1A inhibitors can trigger atrial fibrillation

Approximately 1% of US adults have been diagnosed with atrial fibrillation (Go et al., 2001), and the prevalence increases with age. The fraction caused by food triggers is not known.

Hansson et al. (2004) described interviews with 100 randomly selected Swedish patients seeking hospital care for what was confirmed to be paroxysmal atrial fibrillation. Using a structured questionnaire, patients were asked about possible triggers including foods. Thirty four patients named alcohol, including 26 red wine, 26 spirits, and 16 white wine (multiple responses were allowed). Twenty five patients identified coffee as a trigger. The study also noted onion, nuts, chocolate, and ice cream as triggers cited "by a few patients".

Patton et al. (2005) described interviews with 180 serial subjects with lone atrial fibrillation (AF) at a Massachusetts hospital. All were diagnosed at age 65 or less. In responding to the questions "Are your episodes of AF regularly caused by ...?", 34% indicated "eating", 16% "eating chocolate", 11% soda, 9% coffee, and 4% tea.

4. Discussion

Section 3 covered 19 reports identifying substances leading to human *in vivo* catecholamine increases or reactions likely due to unmeasured catecholamine increases. The cited studies all avoided or controlled for confounding chemicals including caffeine and ethanol. The identified substances, and the sections describing their *in vivo* effects, are summarized in Table 2.

There are a number of reasons that could explain why excess catecholamines have not been linked to SULT1A inhibition. Non-primate mammals have no SULT1A3 ortholog (Riches et al., 2009) so they deactivate catecholamines primarily through glucuronidation using a different enzyme complex (Strott, 2002); if SULT1A3 inhibition is critical to the mechanism in humans, dietary tests in non-primate mammals are unlikely to identify these effects. There are also often confounding chemicals masking the effects, especially caffeine and alcohol, which have their own health impacts. The mechanism works through catecholamines, which are naturally present in the body; differentiating normal catecholamines from those not deactivated because of SULT1A inhibition is not straightforward. A two-step mechanism, requiring both SULT1A inhibition and a catecholamine source, can be difficult to identify and test and can show delayed symptoms. Genetic predisposition to SULT1A inhibition also varies significantly.

4.1. SULT1A genetics

SULT1A1 has three alleles (*1, *2, and *3), with different activities (Nagar et al., 2006). In general, the V_{max} activity is *1 > *3 > *2 across various substrates. There are also ethnic frequency differences; in Whites *1 = 65.6%, *2 = 33.2%, and *3 = 1.2%, for African–Americans *1 = 47.7%, *2 = 29.4%, and *3 = 22.9%, while for Chinese *1 = 91.4%, *2 = 8.0%, and *3 = 0.6%. If SULT1A1 inhibition were a contributor to migraines, reduced starting SULT1A activity would likely make a person more susceptible to inhibition and resulting migraines. For individuals, Littlewood et al. (1982) demonstrated that patients with dietary-triggered migraines had reduced SULT1A activity compared to controls ($p < 0.01$). At the group level, Barnes et al. (2005), show the age-adjusted prevalence of migraines in US adults is lower in Asians than in Whites or African–Americans.

African–Americans also have a SULT1A3 allele (*2) that reduces activity to 28% of the *1 allele found in all tested Caucasians (Thomae et al., 2003); note that alleles of SULT1A4 are not yet known. The *2 allele frequency is relatively low (4.2%). Unfortunately, no information is available on the recessive/dominant characteristics of the SULT1A3 alleles. However, it is clear that African–Americans have significant risk of lower-activity SULT1A compared to Whites or Asians, given the higher frequency and lower-activity of non-*1 alleles. If SULT1A inhibition underlies diabetes (discussed in Section 4.2), it is likely African–Americans would have a higher prevalence of diabetes. In fact, the prevalence of diabetes in African–Americans (10.1%) is higher than in Whites (5.7%) or Asians (5.5%) (Barnes et al., 2005).

Table 2
Sections describing *in vivo* effects of SULT1A Inhibitors.

Substance	Increased Catecholamines	Blood pressure changes	Migraine headaches	Atrial fibrillation
Alcohols (generic)			3.3.2–3.3.3	3.4
Red wine	3.1.2		3.3.1–3.3.3	3.4
Champagne	3.1.2			
White wine			3.3.2	3.4
Spirits			3.3.2	3.4
Citrus fruits	3.1.1		3.3.2	
Orange juice	3.1.1 and 3.1.6	3.2.4		
Hesperidin		3.2.4		
Mixed berries		3.2.3		
Lingonberry juice	3.1.3			
Bananas	3.1.1			
Coffee	3.1.1 and 3.1.5	3.2.1	3.3.2	3.4
Tea	3.1.1 and 3.1.4			3.4
Chocolate	3.1.1		3.3.2	3.4
Ice cream				3.4
Vanilla/vanillin	3.1.1		3.3.4	
Quercetin		3.2.2		
Onion				3.4
Nuts				3.4
Soda				3.4
Cheese			3.3.2	

4.2. Health impacts

The health impacts of SULT1A inhibition are likely significant. The prevalence of migraine was discussed in Section 3.3. Atrial fibrillation will likely increase in prevalence as the population ages. Two additional conditions are hypothesized in this study to be caused by SULT1A inhibition in susceptible patients: "holiday heart" and type 2 diabetes.

Holiday heart is where otherwise-healthy patients develop arrhythmias after excessive alcohol consumption. These arrhythmias may be due to catecholamines (Budzikowski, 2011). It is reasonable to hypothesize that sufficient alcohol-based SULT1A inhibition, combined with a catecholamine source (stress, excitement), can cause holiday heart in susceptible individuals. This mechanism also accounts for two unexplained facets of holiday heart; many binge drinkers do not get arrhythmias, and arrhythmias can begin up to a day after binge drinking. The former could be due to drinking less-effective inhibitors (vodka, gin), lack of a catecholamine source, or favorable SULT1A genetics, while the latter could be caused by the catecholamine source arriving significantly after the start of inhibition.

Pheochromocytoma, with its excess catecholamines, is associated with type 2 diabetes (La Batide-Alanore et al., 2003, and Wiesner et al., 2003). SULT1A inhibition could also lead to type 2 diabetes, by increasing plasma epinephrine. Epinephrine acts to raise glucose levels by triggering glycogenolysis and restricting insulin-stimulated glucose uptake by skeletal muscles (Briscoe and Davis, 2006). Until the excess epinephrine is removed from the system, the person will have increased glucose and insulin concentrations, with insulin resistance building up over time. Chronic partial inhibition over years of moderate levels of SULT1A inhibitor ingestion could slowly reinforce the epinephrine/glucose/insulin behavior, eventually leading to full-blown type 2 diabetes. In a recently completed 18-year study of women, Bazzano et al. (2008) showed that juice consumption including SULT1A-inhibitors orange and grapefruit increased the hazard of diabetes.

4.3. Suggestions for future work

It is important to clarify that SULT1A inhibition does not create free plasma catecholamines. However, if there is a source of catecholamines, SULT1A inhibition will prevent the body from deactivating the catecholamines. This is reinforced in Nicolodi and Sicuteri (Section 3.3.3); it is the combination of alcohol (inhibitor) plus stress (a source of catecholamines) that often leads to the migraine. It can also be seen in Kuchel's pheochromocytoma patient (Sections 3.1.6 and 3.2.4); the patient was asymptomatic in spite of the tumors producing catecholamines, until a SULT1A-inhibitor was ingested. This has important implications for future tests along the lines of those described in Section 3; improved test design would incorporate a catecholamine source along with the inhibitors. A sample of chocolate in a quiet laboratory experiment could inhibit the SULT1A enzymes of a susceptible patient, but without catecholamines there might be no impact. The same chocolate combined with stress could be symptomatic.

The trials described in Section 3 should also be repeated using subgroups based on SULT1A alleles, which could reduce variability in the results. One particular example is the metanephrine testing discussed in Section 3.1.1. The false positive rate in such testing is approximately 18%, and the cause of the high false positive rate has not been conclusively identified (Sawka et al., 2005). One possibility is that a significant fraction of the false positives are due to SULT1A inhibition, possibly with a genetic influence. Combining the current metanephrine test with an identification of SULT1A alleles might reduce the rate of false positives.

These results provide a new lens for examining the longstanding controversy over the health impacts of recreational alcohol. Different alcohols will have different effects on the cardiovascular system, depending on the amounts and types of SULT1A inhibitors. Simple alcohol-equivalence is not sufficient for proper analysis. This was best demonstrated in Sections 3.1.2 and 3.3.1.

Cheese with and without annatto should be tested as a migraine trigger. Pre-diabetes and early-diabetes patients (type 2 diabetes) could be given diets with controlled amounts of SULT1A inhibitors.

Ethnic differences in genetics and disease prevalence provide another useful test. For a sample of American Indian and Alaska Natives, migraine and diabetes prevalences were 22.9% and 13.2% (Barnes et al., 2005), respectively, higher than for other US ethnic groups. If SULT1A inhibition is the underlying cause, it is likely that this is due to higher frequencies of the lower-activity SULT1A alleles. SULT1A genetic data for these groups is not available.

5. Conclusions

There is substantial evidence that some people who ingest SULT1A inhibitors respond with increased plasma catecholamines. In susceptible patients, these catecholamines can impact blood pressure, trigger migraines, and trigger atrial fibrillation. Also in susceptible patients, SULT1A inhibition is hypothesized to lead to "holiday heart" and type 2 diabetes.

There is probably a genetic component to susceptibility to SULT1A inhibition, caused by lower-activity alleles of SULT1A1 and SULT1A3. The genetic differences may be causing significant noise in experiments with SULT1A inhibitors such as described in Section 3. It is recommended that future studies use subgroup analysis based on SULT1A1/1A3 alleles.

Experiments on SULT1A inhibitors should include a source of catecholamines. SULT1A inhibition without catecholamines may be asymptomatic.

SULT1A inhibition may be a key contributor to cheese-induced migraines (via annatto), the false positives in metanephrine testing, and the cardiovascular impacts of recreational alcohols.

Conflict of Interest

The author declares that there are no conflicts of interest.

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