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Effect of psychotropic drug treatment on sterol metabolism

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ABSTRACT

Cholesterol metabolism is vital for brain function. Previous work in cultured cells has shown that a number of psychotropic drugs inhibit the activity of 7-dehydrocholesterol reductase (DHCR7), an enzyme that catalyzes the final steps in cholesterol biosynthesis. This leads to the accumulation of 7-dehydrocholesterol (7DHC), a molecule that gives rise to oxysterols, vitamin D, and atypical neurosteroids. We examined levels of cholesterol and the cholesterol precursors desmosterol, lanosterol, 7DHC and its isomer 8-dehydrocholesterol (8DHC), in blood samples of 123 psychiatric patients on various antipsychotic and antidepressant drugs, and 85 healthy controls, to see if the observations in cell lines hold true for patients as well. Three drugs, aripiprazole, haloperidol and trazodone increased circulating 7DHC and 8DHC levels, while five other drugs, clozapine, escitalopram/citalopram, lamotrigine, olanzapine, and risperidone, did not. Studies in rat brain verified that haloperidol dose-dependently increased 7DHC and 8DHC levels, while clozapine had no effect. We conclude that further studies should investigate the role of 7DHC and 8DHC metabolites, such as oxysterols, vitamin D, and atypical neurosteroids, in the deleterious and therapeutic effects of psychotropic drugs. Finally, we recommend that drugs that increase 7DHC levels should not be prescribed during pregnancy, as children born with DHCR7 deficiency have multiple congenital malformations.

1. Introduction

Cholesterol is an essential component of cellular membranes (Maxfield and Tabas, 2005). As much as 25% of cholesterol and cholesterol derivatives are contained in the human brain, even though the brain accounts for only 2% of total body weight (Dietschy and Turley, 2001, 2004). Although some of the body's cholesterol is derived from nutritional sources, the brain depends predominantly on intrinsic de novo cholesterol biosynthesis as the blood-brain barrier limits the uptake of cholesterol from the circulation (Korade et al., 2009; Nicholas and Thomas, 1961).

Mitochondria play an important role in many aspects of cholesterol metabolism (Tatsuta et al., 2014). Endogenous cholesterol synthesis is essential for brain development, and intact cholesterol metabolism remains critical throughout life for normal brain function. In the elderly, high cholesterol is associated with better memory function, while low cholesterol is associated with an increased risk of depression (Huang and Chen, 2005; You et al., 2013).

Acetyl-CoA, a central player in energy metabolism, is the seed molecule for cholesterol biosynthesis, which in over 20 enzymatic steps leads to cholesterol (Fig. 1). Though the pathway branches at lanosterol, 7-dehydrocholesterol reductase (DHCR7) is crucial in both paths to complete the synthesis of cholesterol. In one branch DHCR7 catalyzes the conversion of 7-dehydrocholesterol (7DHC) into cholesterol, and in the other branch the conversion of 7-dehydrodesmosterol into desmosterol.

A number of psychotropic drugs have been shown to increase 7DHC levels in cell lines (Korade et al., 2016). A preliminary study suggested that patients on aripiprazole or trazodone might have elevated blood levels of 7DHC, indicating DHCR7 inhibition (Hall et al., 2013). However, a comparison and contrast of the effects of a larger group of psychotropic drugs on cholesterol metabolism, levels of 7DHC, and its isomer 8-dehydrocholesterol (8DHC), in patients' blood has not been carried out yet.

Abbreviations: DHCR7, 7-dehydrocholesterol reductase; 7DHC, 7-dehydrocholesterol; SLOS, Smith-Lemli-Opitz syndrome; dhVitD, 1,25-dihydroxyvitamin D; 8DHC, 8-dehydrocholesterol; BHT, butylated hydroxytoluene; TPP, triphenylphosphine; PTAD, 4-phenyl-1,2,4-triazoline-3,5-dione; APCI, atmospheric pressure chemical ionization; SRM, selected reaction monitoring; CID, collision induced dissociation; EPS, extrapyramidal symptoms; IPP, isopentenyl pyrophosphate; Dhcr24, 24-dehydrocholesterol reductase; MDD, Major depressive disorder; BPD, bipolar disorder; SZ, schizophrenia; SA, schizoaffective disorder; SZ+, SZ, SA and schizophreniform disorder.

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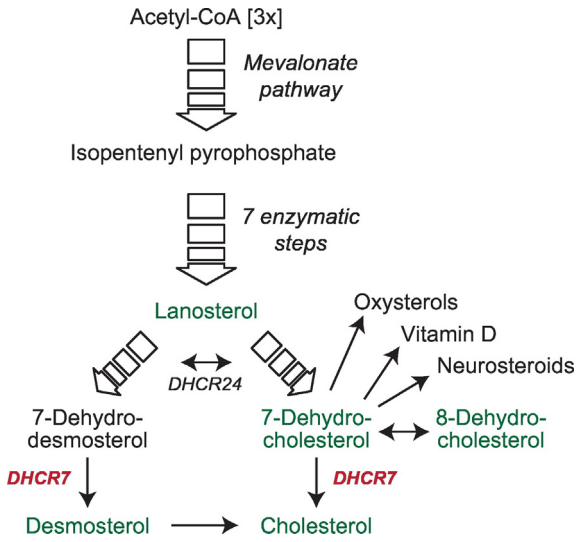

Fig. 1. Synthesis of cholesterol, 7DHC and vitamin D. Cholesterol synthesis commences with 3 molecules of acetyl-CoA, which in the mevalonate pathway are converted to isopentenyl pyrophosphate (IPP). IPP gives rise to lanosterol in a series of enzymatic reactions. Two separate enzymatic pathways generate cholesterol from lanosterol. Metabolites from both pathways are interconvertible via 24-dehydrocholesterol reductase (Dhcr24). For detailed metabolic pathway information see (Sharpe and Brown, 2013). Metabolites measured in the current study are shown in green, important enzymes are shown in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Much of the current knowledge about DHCR7 comes from research of Smith-Lemli-Opitz syndrome (SLOS), caused by mutations in the DHCR7 gene. SLOS is characterized by altered CNS structure and function, manifested in developmental disabilities and autism (Bukelis et al., 2007; Nowaczyk and Irons, 2012). While cholesterol deficiency likely plays a central role in the disease, so might be the accumulation of 7DHC and 8DHC, the ensuing lipid peroxidation, and the formation of oxysterols (Liu et al., 2013; Xu et al., 2009). SLOS studies point to an important function of DHCR7 and cholesterol particularly during early brain development. Curiously, the disproportionate frequency of a small number of null alleles in SLOS has raised the possibility that decreased DHCR7 activity and increased levels of 7DHC confer an evolutionary advantage in heterozygous individuals, despite the devastating effects of homozygous mutations (Witsch-Baumgartner et al., 2000).

A competitive advantage of increased 7DHC levels could rest in its role as the sole source for endogenously synthesized vitamin D3 (cholecalciferol). Since polymorphisms in DHCR7 are associated with vitamin D levels, it has been suggested that higher concentrations of 7DHC might be protective against hypovitaminosis (Wang et al., 2010). Vitamin D deficiency is prevalent in Western populations and has been associated with memory function, depression, and psychosis (Anglin et al., 2013; Crews et al., 2013; Holick, 2009; McGrath et al., 2010). The presence of the vitamin D receptor in the brain indicates a role for vitamin D in brain function (Eyles et al., 2005). Moreover, the biologically active form of vitamin D, a metabolite of 7DHC and ligand for the vitamin D receptor, 1,25-dihydroxyvitamin D (dhVitD), mediates a diverse array of neuroprotective functions (Garcion et al., 2002).

Mitochondrial enzymes cleave 7DHC into novel, neurosteroid-like compounds (Acimovic et al., 2016; Marcos et al., 2004). Although neurosteroids were initially described as nuclear receptors that activate specific genetic programs, it is now accepted that they can also modulate neuronal excitability by rapid, non-genomic actions (Compagnone and Mellon, 2000; Omura, 2006; Slominski et al., 2015). Neurosteroids can have mood-stabilizing, anxiolytic, anticonvulsive and antidepressant effects, through modification of GABA and glutamate systems in the brain (Dubrovsky, 2005; Reddy et al., 2004; Zorumski et al., 2013). However, dependent on type, concentration and brain area in which they accumulate, they can also have the opposite effect (Dubrovsky, 2005). Thus, the effect of neurosteroids synthesized from elevated 7DHC on brain function is currently unknown.

Accumulation of 7DHC can also have negative consequences. As the clinical manifestations of SLOS demonstrate, disruption of DHCR7 activity, particularly during early development, has deleterious effects on brain function. While its role as a precursor for cholesterol, vitamin D and neurosteroids might be beneficial for brain function, 7DHC and 8DHC are a source of lipid peroxidation and oxysterols (Liu et al., 2013; Xu et al., 2009). Of relevance to treatment with psychotropic drugs, oxysterols have been associated with metabolic syndrome, a side effect of treatment with psychoactive drugs manifested in cardiovascular disease and obesity (Guillemot-Legris et al., 2016). Moreover, cellular stress caused by lipid peroxidation might contribute to the extrapyramidal side effects in the brain caused by treatment.

At this point, we are in need of more information about psychotropic drug effects on cholesterol metabolism and accumulation of 7DHC in patients. Understanding the individual profiles of psychotropic drugs is the first step toward determining if protection against lipid peroxidation and oxysterols in patients on these drugs can mitigate side effects, on one hand, and if an increase in vitamin D levels or formation of particular neurosteroids might contribute to the therapeutic profile, on the other. Furthermore, as the experience with SLOS shows, we need to identify which drugs inhibit DHCR7 activity and limit their prescription during pregnancy.

2. Materials and methods

2.1. Materials

Unless otherwise noted, all chemicals were purchased from Sigma-Aldrich Co (St. Louis, MO). HPLC grade solvents were purchased from Thermo Fisher Scientific Inc. (Waltham, MA). [25,26,26,26,27,27,27-d_7] 7-DHC and 8-DHC were obtained by chemical synthesis as previously described (Anastasia et al., 1981; Xu et al., 2011b).

2.2. Study participants

One hundred twenty-three patients with a psychiatric disorder (21 with major depressive disorder, MDD; 22 with bipolar disorder, BPD; and 80 with schizophrenia, SZ, schizoaffective disorder, SA, or schizophreniform disorder, grouped together into SZ+) were recruited through the inpatient unit and outpatient clinic at the Vanderbilt Psychiatric Hospital, and 85 healthy controls were recruited via advertisements within the community (Table 1). The study was approved by the Vanderbilt University Institutional Review Board and all study subjects provided written informed consent. All participants were administered the Structured Clinical Interview for the DSM-IV-TR (SCID), which was reviewed by an experienced psychiatrist. Participants with any significant medical or neurological disease, head injury or a history of drug dependence, were excluded. The Vanderbilt Psychiatric Hospital has a detailed protocol to assess and verify diagnoses of study participants, and to capture clinical, psychological and demographic data (Sheffield et al., 2013; Woodward and Heckers, 2015).

2.3. Medication history

The medication history was based on self-report, and included current and prior medication. When available, the research group at the Vanderbilt Psychiatric Hospital cross-referenced the supplied information with current medical records. Despite best efforts, medication nonadherence, a well-known challenge in psychotic disorders, might have occurred in some instances (Chapman and Horne, 2013).

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