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Bile in the Brain? A Role for Bile Acids in the Central Nervous System

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Bile acids were classically viewed as detergents whose main function is to aid in the breakdown of dietary lipids. This is achieved by the formation of mixed micelles with cholesterol and other phospholipids [1]. It is now greatly appreciated that bile acids are more complex than mere detergents, and should actually be viewed as steroid hormones. Like many other steroid hormones such as neurosteroids and glucocorticoids, bile acids are synthesized from the conversion of cholesterol to various bile acids. The "classical pathway" of bile acid synthesis is achieved through the enzymatic activity of the cytochrome P450 family of proteins, namely cholesterol 7α-hydroxylase (Cyp7a1), which is responsible for the 7α-hydroxylation of cholesterol [2]. Historically, bile acid synthesis has been thought to occur solely in the liver, as Cyp7a1 is a liver-specific enzyme, however, an alternative or "acidic pathway" was discovered which starts with the side chain 27-hydroxylation catalyzed by Cyp27a1 [3]. Interestingly, Cyp27a1 is expressed in an array of extrahepatic tissues such as kidney [4], immune cells [5], and the brain [6] and mutations in the Cyp27a1 gene has been shown to underlie the sterol storage disorder cerebrotendinous xanthomatosis, which leads to cholesterol accumulation in the brain and neurological dysfunction [6]. The development of neurological dysfunction by the mutation of a key enzyme in bile acid biosynthesis poses the question of whether bile acids (or their intermediaries) play a physiological role in the brain under homeostatic conditions. It is now well respected that during conditions of liver dysfunction such as cholestatic liver disease (primary sclerosing cholangitis or primary biliary cirrhosis) bile acids are dramatically increased in the circulation [7] and can gain access to brain [8]. Controversy still remains however, as to whether bile acids are present in the brain and play a physiological role in a non-diseased state.

Evidence for the notion that bile acids are present in the brain during homeostatic conditions came with the finding by Mano et al. [9] that the rat brain contains unconjugated primary and secondary bile acids in the absence of any liver injury. In this study it was found that the primary bile acid CDCA composed ~ 95% of total brain bile acid composition with CA and DCA being around 2-3% [9]. This work elegantly led to the speculation that the bile acids found in the brain under normal physiological circumstances are in fact synthesized locally and not from hepatic origin since the brain levels are approximately 10-fold higher than circulating levels [9]. Interestingly, CDCA was found to be ~10 more abundant than the prototypical neurosteroids pregnenolone [9], suggesting that bile acids could in fact be another class of neuroactive steroids. Further evidence for the idea that bile acids are endogenous molecules to the CNS was highlighted by the finding that in humans the most abundant oxysterols are the C_{27} and C_{24} intermediates of bile acid synthesis [10]. The finding that the most abundant oxysterols present in CSF of humans are bile acid intermediates supports the notion that the alternative or "acidic" pathway for bile acid synthesis occurs in the brain with the conversion of 27-hydroxycholesterol to 7-hydroxy-3-oxocholest-4-en-26-oic acid [11].

If bile acids act in a physiological manner in the brain then the signaling machinery necessary for bile acids to exert their actions must be present in the brain. In the liver, bile acids are very promiscuous molecules and activate both nuclear receptors (farnesoid X receptor [FXR], vitamin D receptor [VDR], pregnane X receptor [PXR], and constitutive androstane receptor [CAR]) [12] and g-protein coupled receptors (TGR5) to exert an array of functions such as controlling inflammation [13] and regulating cholesterol metabolism [14]. The g-protein coupled receptor TGR5 has recently been shown to be expressed in various regions of the brain and to act as a neurosteroid receptor [15]. This raises the possibility of cross talk between neurosteroids and bile acids, possibly to alter neurotransmission. Neurosteroids classically act to modulate GABAergic tone [16], and in fact, the bile acids ursodeoxycholic acid (UDCA) and chenodeoxycholic acid (CDCA) has been shown recently to antagonize $GABA_A$ receptors [17,18] and CDCA was shown to antagonize NMDA receptors [18]. This is further evidence supporting the idea that bile acids could be playing an endogenous role in the CNS.

As with all signaling pathways, there is the potential for dysregulation during disease states and bile acids are no exception. While studies examining the dysregulation of the bile acid signaling system in the CNS during different pathologies are lacking, studies have been conducted looking at bile acids as a potential therapeutic agent for various neurological disorders. These studies revealed that bile acids exert neuroprotective effects in models of Huntington's disease [19] and Alzheimer's disease [20,21]. The results of these studies indicate, at the very least, bile acid signaling machinery is present in CNS.

Our understanding of bile acids as a molecule has undergone a vast renaissance in the past several decades. We have gone from viewing bile acids as mere detergents synthesized in the liver to breakdown dietary lipids to discovering that bile acids act as signaling molecules in the liver [14]. This breakthrough has led to the idea that perhaps bile acids could potentially exert their signaling capabilities to extrahepatic tissues. Of particular interest has been the possibility of bile acids acting as signaling molecules in the brain. The idea of bile acids being solely synthesized in the liver has been challenged by the finding that Cyp27a1, a crucial enzyme in the "acidic" pathway of bile acid synthesis is expressed in the brain and when mutated leads to neurological defects [6]. The brain's main mechanism of clearing cholesterol is through the enzymatic activity of Cyp46a1 which synthesizes 24S-hydroxycholesterol which then diffuses across the blood brain barrier [22]. Interestingly,

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24S-hydroxycholesterol is a substrate for Cyp7b1, another enzyme in the bile acid biosynthetic pathway [23]. The fact that bile acid synthesis enzymes (Cyp27a1) and their intermediates (24S-hydroxycholesterol) are present during the brain coupled with the finding that bile acids are found endogenously in the CSF and brain [9,10] supports a strong case for bile acids to be endogenously synthesized in the CNS. It is now widely appreciated that bile acids are pleiotropic signaling molecules in the body, and the presence of receptors and synthesis enzymes in the CNS indicates that bile acids could in fact be an endogenous signaling system present in the brain. Further studies are crucial to dissect this signaling pathway under both physiological and pathophysiological states.

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