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Review article

Lipids in psychiatric disorders and preventive medicine

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ABSTRACT

Psychiatric disorders like mood disorders, schizophrenia, or drug addiction affect a sizeable proportion of the human population and severely compromise quality of life. Therefore, measures to prevent the manifestation, and treatments to ameliorate the symptoms, of these disorders are in high demand. Brain lipids determine the localization and function of proteins in the cell membrane of neurons. Lipids may also act as neurotransmitters or other signalling molecules. The lipid composition of the brain can be influenced by nutrition, environmental factors, and by behavioural activity. Thus, lipids represent a target for preventive medicine of psychiatric disorders. Here we review how brain lipids contribute to normal behaviour and to major psychiatric disorders with the focus on phospholipids/fatty acids, sphingolipids, and endocannabinoids. Accumulating evidence suggests a crucial role for membrane forming and signalling lipids in the brain in the etiopathologies of depression, bipolar disorders, schizophrenia, and drug addiction. Lipids also represent potential preventive interventions for these psychiatric disorders by either targeted dietary supplementation or pharmacological manipulation of lipid regulating enzymes.

Contents

Abbreviations: AA, arachidonic acid (20:4n-6); ABHD, α,β-hydrolase; AC, acid ceramidase; AEA, *N*-arachidonoylethanolamide; 2-AG, 2-arachidonoylglycerol; AD, Alzheimer's disease; ALA, α-linolenic acid (18:3n-3); ASM, acid sphingomyelinase; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CBD, cannabidiol; CB1R, cannabinoid receptor type 1; CB2R, cannabinoid receptor type 2; CerS, ceramide synthase; CNS, central nervous system; COX, cyclooxygenase; CPT1C, carnitine palmitoyltransferase 1C; CREB, cAMP response element binding protein; CSF, cerebrospinal fluid; DAG, diacylglycerol; DEA, *N*-docosatetraenoylethanolamine; DHA, docosahexaenoic acid (22:6n-3); DPA, docosapentaenoic acid (22:5n-6); eCB, endocannabinoid; EFA, α-linolenic acid (18:3n-3); EPA, eicosapentaenoic acid (20:5n-3); ERK, extracellular-signal regulated kinase; FAAH, fatty acid amide hydrolase; GalCer, galactosylceramide; GluCer, glucotosylceramide; GPCR, G-protein-coupled receptors; HEA, *N*-homo-γ-linolenoylethanolamine; HPA, hypothalamic-pituitary-adrenal; 5-HT, serotonin; IFNα, interferon-α; LacCer, lactosylceramide; MAGL, monoacylglyerol lipase; MCI, mild cognitive impairment; MR, magnet resonance; Nacc, nucleus accumbens; NADA, *N*-arachidonoyl-dopamine; NAPE-PLD, *N*-acylphosphatidylethanolamine-specific phospholipase D; NArPE, *N*-arachidonoylphosphatidyl-ethanolamines; NC, neutral ceramidase; NMDA, *N*-methyl-D-aspartate; NSM, neutral sphingomyelinase; OEA, oleoylethanolamide; PC, glycerophosphocholine; pCPA, *p*-chlorophenylalanine; PCP, phencyclidine; PE, phosphatidylethanolamine; PEA, palmitoylethanolamide; PFC, prefrontal cortex; PI, phosphatidylinositol; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; SNP, single nucleotide polymorphism; S1R, sigma 1 receptor; Sph, sphingosine; S1P, sphingosine-1-phosphate; SphK2, sphingosine kinase 2; SPT-1, serine palmitoyl transferase 1; THC, Δ9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid receptor type 1; VMAT2, vesicular monoamine transporter2; VTA, ventral tegmental area.

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1. Introduction

Mental function in mammals involves the sensation and perception of sensory stimuli, analysis of perceived information, and subjective emotional and behavioural responses to the perceived stimuli and information. It also includes how information is processed by cognitive activity, how it is stored in memory systems, and how it is retrieved on demand. Together, these processes determine how an organism perceives itself and how it interacts with its environment and conspecifics. Deviation in one or more dimension of mental activity from what is perceived as 'normal' constitutes psychological disturbances and psychiatric disorders (Schumann et al., 2014). The anatomical substrate of mental activity is the brain, which operates in close interaction with all other organs of the body (O'Mahony et al., 2015). As in peripheral organs, function of the brain depends on nutrient supply. Over time, even small changes in nutrition may affect microstructure and activity of the brain in various ways. This may eventually affect functions as complex as 'personality', in keeping with the proverbial consequence of "Du bist, was Du isst" (you are what you eat; Ludwig Feuerbach). Thus, nutrition contributes not only to physical well-being, but also mental health; whereas malnutrition, which is essentially defined by its consequences, can contribute to mental illness. In contrast, there are certain diets that may counteract and even reverse psychiatric problems induced by other factors, such as stress (Bergouignan et al., 2009).

A major class of molecules that fundamentally determine cell function in the brain are lipids. Lipids and/or their precursors derived from food are taken up by the organism and used for the maintenance of general cell function. In particular, the integrity of cell membranes and signalling through membranes depend on lipid homeostasis in the brain. Studies published in recent years have provided new insights into how lipid homeostasis, most notably of phospholipids, sphingolipids, and endocannabinoid lipids, affects mental functions. These findings serve as the basis for a preventive medicine approach for psychiatric disorders by which the risk for developing psychiatric disorders may be mitigated by interventions that modulate lipid homeostasis in the brain. Evidence supporting this approach is reviewed here.

2. Targeting psychiatric disorders by preventive medicine

2.1. What is preventive medicine and its application in psychiatric disorders

A number of serious psychiatric disorders tend to emerge during critical neurodevelopmental periods, such as adolescence, and often lead to protracted illness phases with significantly reduced quality of life. Efforts aimed at the prevention of mental disorders include reducing incidence, prevalence, and preventing or delaying recurrence; limiting the duration of symptoms; and decreasing the impact of illness in the affected person, their families and society (Mrazek and Haggerty, 1994). Prevention is important when aim-