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Original Research

SREBP and central nervous system disorders: genetic overlaps revealed by *in silico* analysis

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Abstract

Background: The central nervous system (CNS) is enriched in lipids; despite this, studies exploring the functional roles of lipids in the brain are still limited. Sterol regulatory element binding protein (SREBP) signaling is a transcriptomic pathway that predominantly participates in the maintenance of lipid homeostasis; however, its involvement in the CNS dysfunction is not well-established. In this study, we aimed to characterize and pinpoint specific genes of the SREBP pathway which may be implicated in neurodegenerative, neurological, and neuropsychiatric diseases. **Methods**: *In silico* bioinformatic analysis was performed using the open-source databases DisGeNET and MSigDB. Protein-protein interaction data were visualized and analyzed using STRING, after which GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analyses were conducted via DAVID (Database for Annotation, Visualization and Integrated Discovery). **Results**: Several common genes were identified between the SREBP pathway and CNS disorders. In GO enrichment analysis, the most enriched biological processes included lipid, cholesterol, and steroid biosynthetic processes; the most enriched molecular functions were transcription factor-related; and the most enriched subcellular compartments revealed that the genes involved in CNS disorders were mainly associated with the enzyme complexes of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN). In KEGG enrichment analysis, the most enriched pathway was the AMP-activated protein kinase (AMPK) signaling pathway, and the top-ranked genes significantly enriched under this pathway were *ACACA*, *ACACB*, *FASN*, *HMGCR*, *MTOR*, *PPARGC1A*, *PRKAA1*, *SCD*, *SIRT1*, and *SREBF1*. **Conclusions**: The findings of this study strengthen the evidence linking the involvement of lipid homeostasis in CNS functions. We suggest herein the roles of downstream ACC and FASN enzymes and upstream AMPK signaling in the SREBP pathway as mechanisms underlying neurodegenerative, neurological, and neuropsychiatric CNS disorders.

Keywords: AMPK; Lipids; Neurodegenerative; Neurological; Neuropsychiatric; SREBP

1. Introduction

Lipids serve various functions in animals. They act as sources of energy and are components of cellular membranes as well as being substrates of compounds participating in diverse biological activities, including steroid hormones, vitamins, bile acids, and eicosanoids [1,2]. Both dietary and endogenous synthetic pathways provide the lipids we require [3,4]. Fatty acid (FA) and cholesterol synthesis can occur in every cell; however, these processes are particularly essential in the liver and adipose tissues, which are organs that specialize in lipid export and storage [5,6]. A class of transcription factors known as sterol regulatory element binding proteins (SREBPs) regulates both cholesterol and FA biosynthesis. SREBPs trigger a series of enzymes essential for endogenous cholesterol, FA, triglyceride (TG), and phospholipid production. SREBPs are thus thought to be key regulators of cholesterogenesis and lipogenesis [3].

SREBPs are transcription factors with a basic-helix-loop-helix-leucine zipper (bHLH-LZ) structure; they are synthesized as 1150 amino acid (aa) inactive precursors attached to the endoplasmic reticulum (ER) membrane [7]. Each SREBP precursor is divided into three domains: (a) a 480-aa NH_2-terminal domain containing the transactivation domain, a serine- and proline-rich region, and the bHLH-LZ region for DNA binding and dimerization; (b) two hydrophobic transmembrane spanning segments, interrupted by a 30-aa short loop that projects into the ER lumen; and (c) a 590-aa COOH-terminal containing the regulatory domain [3,8] (Fig. 1). The ER-anchored SREBP precursor undergoes a two-step cleavage event after activation to produce the NH2-terminal active domain, which is known as the nuclear form of SREBP (nSREBP). The bHLH-LZ domain has a novel nuclear localization signal that binds directly with importin and allows nSREBPs to enter the nucleus [9–11]. Once translocated into the nucleus, nSREBPs stimulate the expression of several genes associated in cholesterogenesis and lipogenesis.

SREBP family members have been identified in numerous mammalian species: SREBP-1a and 1c, which are generated from a single gene (sterol regulatory element binding transcription factor 1; *SREBF-1*) on human chromosome 17p11.2 [12], and SREBP-2, which is produced

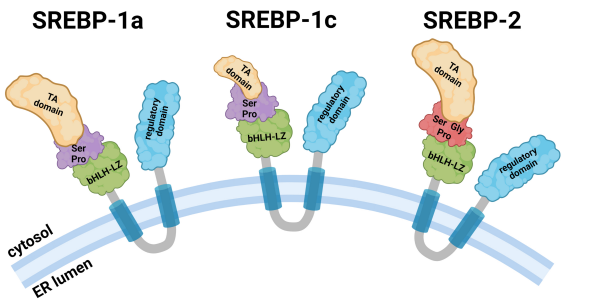

Fig. 1. Schematic structure of SREBP precursors. Each SREBP precursor is divided into three domains: (1) a 480-aa NH2-terminal domain containing the transactivation domain, a serine and proline-rich region, and the bHLH-LZ region for DNA binding and dimerization; (2) two hydrophobic transmembrane spanning segments, interrupted by a 30-aa short loop that projects into the ER lumen; and (3) a 590-aa COOH-terminal containing the regulatory domain. Abbreviations: bHLH-LZ, basic helix-loop-helix leucine zipper; ER, endoplasmic reticulum; Gly, glycine; Pro, proline; Ser, serine; SREBP, sterol regulatory element binding protein; TA, transactivation.

from a different gene (*SREBF-2*) on human chromosome 22q13 [13]. SREBP-1 and SREBP-2 proteins have 47% similarity. The first exons of SREBP-1a and 1c transcripts differ owing to different transcription start locations (exon 1a and exon 1c, respectively), whereas the remaining exons are shared by both isoforms [8,14]. Moreover, alternative 3′-end splicing has been observed in humans (exons 18a and 19a or 18c and 19c) [15]. Additionally, adipocyte determination and differentiation dependent factor 1 (ADD1) was the term originally given to the SREBP-1c rat homolog because of its role in adipogenesis [16]. Owing to its larger NH2-terminal transactivation domain, SREBP-1a is a more effective transcriptional activator than is SREBP-1c. The latter is the most prevalent isoform in mouse and human tissues, with particularly high levels in the liver, white adipose tissue, skeletal muscle, adrenal gland, and brain, whereas SREBP-1a, in contrast, is widely expressed in cell lines and tissues with high cell proliferation capacity, such as spleen and intestinal tissues [17].

Even though lipids are highly enriched in the brain [18–22], there is little research identifying and examining the role of lipids in brain structure and function. This matter has been acknowledged by some neuroscientists. For example, Montesinos, Guardia-Laguarta and Area-Gomez [18] have proposed numerous reasons for this obvious gap in knowledge: (1) lipids are not coded in the genome, and hence are not subject to the core dogma of biology, but rather to the rules of biophysics; (2) lipids do not possess intrinsic catalytic activity, and as a result, they have long been thought to be inert substances with little biological value or only a reflection of food and environmental adaptations; and (3) lipids cannot be studied as separate molecules. To maintain homeostasis and retain the form and function of cellular membranes, fluctuations in the proportion of one lipid typically trigger a cascade of changes in other lipid species. Thus, a large amount of the information carried by lipids must be investigated holistically. Collectively, these and other factors have driven lipid biology out of the 'mainstream' of neuroscience research.

Nevertheless, lipid research in neuroscience has been increasing, indicating that neural lipids are finally receiving the attention that they deserve [23]. This could be due to the emergence of novel technologies such as mass spectrometry [24,25] and atomic-force microscopy [26]. These methods allow for the detailed screening of complex changes in lipid composition as well as the characterization of the topographical distribution of lipid species in the brain, down to the level of individual neuronal cells [18].

Lipids have an established set of roles that are equivalent with those of neurotransmitters, neuropeptides, and growth factors [27]. Specifically, lipids play key roles in structural activities (i.e., membrane compartmentalization) [28] and physiological functions (i.e., energy production, gene expression, neural communication, neurogenesis, synaptic transmission, as well as signal transduction and regulation) [29]. Other roles include the processing of complex behaviors and participation in neocortex development [19,30,31]. In neurons, synapses and neuromuscular junctions are specific sites wherein lipid dynamics regulate cellular activities, such as signal transduction and transmembrane gradients [30]. For example, changes in cholesterol and sphingolipids are required to produce membrane curvature for synaptic vesicle release and fusion, ion channel modulation, and protein activation signaling [32]. In glial cells, lipids are important components of oligodendrocytes, where they function in myelin biogenesis, axon-glia communication, and long-term maintenance of myelin [33]. Lipids in astrocytes play important roles in energy generation, membrane fluidity, and cell-to-cell signaling [34]. In microglia, increased lipid metabolism is vital in supporting protective cellular functions, such as phagocytosis [35] and neuroinflammatory sensitization of central pain pathways [36].

Central nervous system (CNS) disorders, including neurodegenerative, neurological, and neuropsychiatric disorders greatly impact quality of life and present an economic burden on society. These disorders are of major clinical importance because their definitive pathoetiology and therapeutics remain largely elusive. Alterations in lipid metabolism in the CNS have recently been implicated in the development of neurodegenerative diseases, mental disorders, and brain injury. Several review papers have described and detailed the crucial role of lipids in tissue physiology and cell signaling in CNS-related diseases

[21,28,37–41]. Adibhatla and Hatcher [21,22] have identified CNS injuries that implicate aberrations in lipid systems. Neurological disorders affected by lipid signaling include bipolar disorder and schizophrenia, and neurodegenerative disorders involving deregulated lipid metabolism include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS). CNS injuries involving altered lipid metabolism include stroke, traumatic brain injury, and spinal cord injury (SCI) [22].

Lipid-related mechanisms involved in CNS disorders include alterations in cholesterol and lipid homeostasis (AD [42,43]), decreased docosahexaenoic acid levels (MS, epilepsy, and stroke [44]), excessive accumulation of cholesterol and sphingolipids (increased activity of phospholipases A2 and generation of lipid mediators (AD [45, 46], PD [45], MS [45], schizophrenia [47], and stroke [48]), increased lipid peroxidation (AD [49], ALS [50]), inhibition of SREBP-1 (schizophrenia [51–54]), lipid raft interaction with amyloid precursor protein (AD [55]), polyunsaturated FAs promoting the aggregation of α-synuclein (PD [56]), and decreased membrane arachidonic acid levels (schizophrenia [47]).

SREBP signaling is a vital pathway responsible for maintaining transcriptional activities that promote lipid synthesis and homeostasis. Even though ample evidence of the associations between lipid deregulation and CNS disorders exists, studies exploring the possible involvement of the SREBP pathway in the development or occurrence of common CNS disorders are not well-established. Instead, most of the studies exploring this pathway have remained focused on disorders of lipid-rich tissues and lipid-regulating organs, such as adipose tissues and the liver, respectively. This warrants a need to discover specific lipid-processing pathways involved in CNS disorders. Thus, we sought to fill this gap in knowledge by conducting *in silico* bioinformatic analyses between the SREBP signaling pathway and CNS disorder-related genes and proteins. We accessed several open-source bioinformatic programs and open-source databases for gene data sets to discover overlaps in protein-protein interactions, gene ontology, and biological functions between CNS disorder-related genes and components of the SREBP signaling pathway.

2. Materials and methods

Fig. 2 shows the schematic diagram of the *in silico* analysis performed in the study.

2.1 Data preparation

Related genes of CNS disorders previously associated with lipid deregulation were exported from the DisGeNET database [57]. DisGeNET is a publicly available collection of genes and variants associated with human diseases. Gene set enrichment analysis (GSEA v4.1.0, Broad Institute, Cambridge, MA, USA) is a computational method

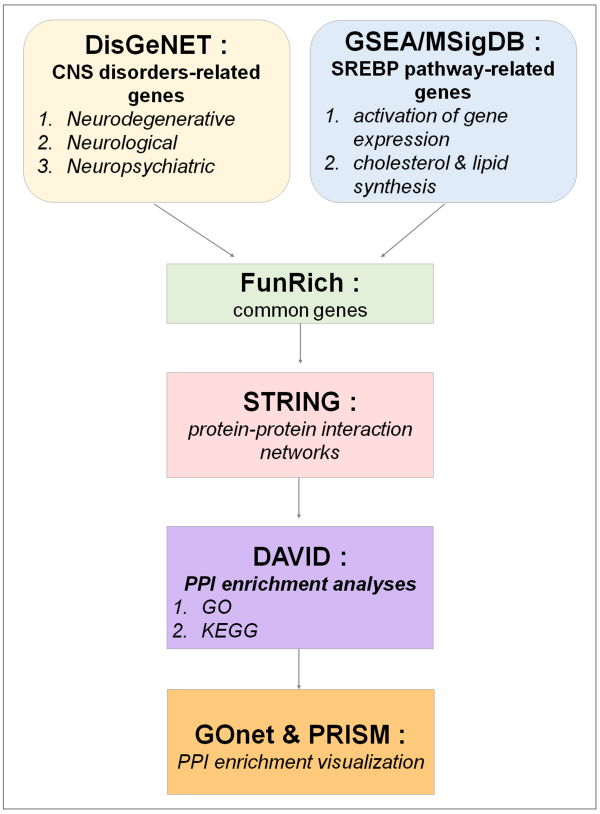

Fig. 2. Schematic diagram of the *in silico* analysis performed in this study. The methodology used in the study are outlined in flow-chart form. Genes related to CNS disorders were obtained from DisGeNET, and SREBP pathway-related genes were collected from the MSigDB feature of GSEA. Overlapping genes between datasets were identified using the FunRich program. The resulting gene sets were uploaded into STRING to obtain protein-protein interactions. Gene set enrichment analyses were conducted using DAVID for GO functional enrichment and KEGG pathway enrichment analyses. Abbreviations: CNS, central nervous system; DAVID, Database for Annotation, Visualization and Integrated Discovery; FunRich, Functional Enrichment analysis tool; GO, Gene Ontology; GSEA, Gene Set Enrichment Analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes; MSigDB, Molecular Signatures Database; PPI, protein-protein interaction; STRING, Search Tool for Retrieval of Interacting Genes.

that statistically analyzes significant differences in gene sets under two biological states. The Molecular Signatures Database (MSigDB v7.4, Broad Institute, Cambridge, MA, USA) [58] is a collection of annotated gene sets utilized by the GSEA software. Genes involved in the SREBP signaling pathway were obtained from the MSigDB collection for GSEA [59]. Common genes between CNS disorder-related set and the SREBP pathway were retrieved using Functional Enrichment analysis tool (FunRich v3.1.4, La Trobe University, VIC, Australia) [60]. FunRich is an open-source program for analyzing gene and protein functional enrichment and interaction networks.

2.2 Protein-protein interaction data

Associations between overlapping gene sets were revealed by constructing a protein-protein interaction (PPI) network using the Search Tool for Retrieval of Interacting Genes (STRING) database [61,62]. STRING is a well-known database that gathers, integrates, and assesses all available PPI data from various sources, as well as computational predictions. Its purpose is to create a massive network that is comprehensive and objective, with both direct (physical) and indirect (functional) linkages. The combined STRING score represents the estimated confidence of data support presented by seven networks, including three genomic context prediction channels (gene neighborhoods, cooccurrence, and fusions), as well as co-expression, experiments, databases, and text-mining channels. Owing to its extensive and up-to-date data, user-friendly website, and uniform scoring method, STRING is regarded as a useful and beneficial tool for static PPI analysis. All seven STRING channels were utilized in this study. PPI networks were generated with *Homo sapiens* as the species of interest, medium confidence of $\geq$0.400 for the minimum required interaction score, nodes corresponding to proteins, and edges representing protein-protein associations.

2.3 GO and KEGG enrichment analyses

To characterize and explore the potential biological functions of CNS disorder-associated genes of the SREBP pathway, the Database for Annotation, Visualization and Integrated Discovery (DAVID) [63,64] was utilized for Gene Ontology (GO) [65,66] function and Kyoto Encyclopedia of Genes and Genomes (KEGG) [67] pathway enrichment analyses. The GO database is a bioinformatics tool that provides specific definition describing gene products in terms of biological process, molecular function, and cellular component. KEGG is a database that contains information on genomes, biological pathways, diseases, medications, and chemical compounds. The functional enrichment analysis results were visualized using GOnet [68] and GraphPad Prism (GraphPad Prism version 8.0.0 for Windows; GraphPad Software, San Diego, CA, USA; www.graphpad.com).

3. Results

3.1 Overview of SREB pathway signaling genes associated with CNS disorders

Gene sets associated with 11 CNS disorders previously reported to be related with lipid deregulatory mechanisms were obtained from the DisGeNET database. The gene sets were divided into three categories, namely (1) neurodegenerative disorder (NDDs): AD, HD, MS, and PD; (2) neurological disorder (NLDs): epilepsy and ischemic stroke; and (3) neuropsychiatric disorder (NPDs): anxiety, bipolar disorder, mental depression, post-traumatic stress disorder (PTSD), and schizophrenia. A total of 17,626 genes were identified, of which 8253, 2374, and 6999 were associated with NDDs, NLDs, and NPDs, respectively.

Two SREBP pathway gene sets were identified from the MSigDB dataset: the SREBP activation of gene expression (SAGE) pathway, which generated 42 genes, and the SREBP cholesterol and lipid homeostasis (SCLH) pathway, which generated 19 genes. The complete lists of gene sets per disorder and pathway are provided in **Supplementary Tables 1** and **2**. After importing the data into FunRich, an analysis of overlapping genes between CNS disorder-related genes and the SAGE pathway was conducted, yielding 25 genes (NDDs: 19, NLDs: 10, NPDs: 11) (Fig. 3A, left panel); the analysis of overlapping genes with the SCLH pathway generated 15 genes (NDDs: 14, NLDs: 8, NPDs: 11) (Fig. 3B, left panel).

In Table 1, a detailed list of SREBP pathway-related genes associated with CNS disorders has been provided. In Table 2, the percentages of common genes ('FunRich recognized' in **Supplementary Table 1**) between SREBP pathways and CNS-related disorders have been presented. Among NDDs, PD (0.54%) exhibited the highest percentage of SREBP pathway-related genes in SAGE, while HD (0.78%) exhibited the highest percentage in SCLH pathways. Among NLDs, epilepsy (0.54%) presented the highest percentage of SAGE pathway-related genes, and ischemic stroke (0.79%) exhibited the highest percentage of common SCLH pathway genes. Among NPDs, mental depression displayed the highest percentage of common genes for both the SAGE (0.52%) and SCLH (0.59%) pathways.

3.2 Interaction networks between SREB pathway signaling genes associated with CNS disorders

Gene product interactions between both SREB pathways and CNS disorders were constructed using STRING (Fig. 3, right panels). The resulting SAGE pathway-related CNS disorder genes PPI network had 25 nodes with 159 edges (*vs.* 8 expected edges), a clustering coefficient of 0.798, an enrichment *p*-value of $<1.0 \times 10^{16}$, and an average node degree of 12.7 (Fig. 3A, right panel). The PPI network of SCLH pathway-related CNS disorder genes had 15 nodes with 77 edges (*vs.* 6 expected edges), a clustering coefficient of 0.869, an enrichment *p*-value of $<1.0 \times 10^{16}$, and an average node degree of 10.3 (Fig. 3B, right panel). The top five genes garnering the highest degree of connectivity were *HMGCR*, *SREBF1*, *SREBF2*, *FASN*, and *PPARA* for the SAGE pathway, as well as *SREBF1*, *SREBF2*, *PPARA*, *PPARGC1A*, and *FASN* for the SCLH pathway. The detailed list of genes and the corresponding interaction information are provided in **Supplementary Table 3**.

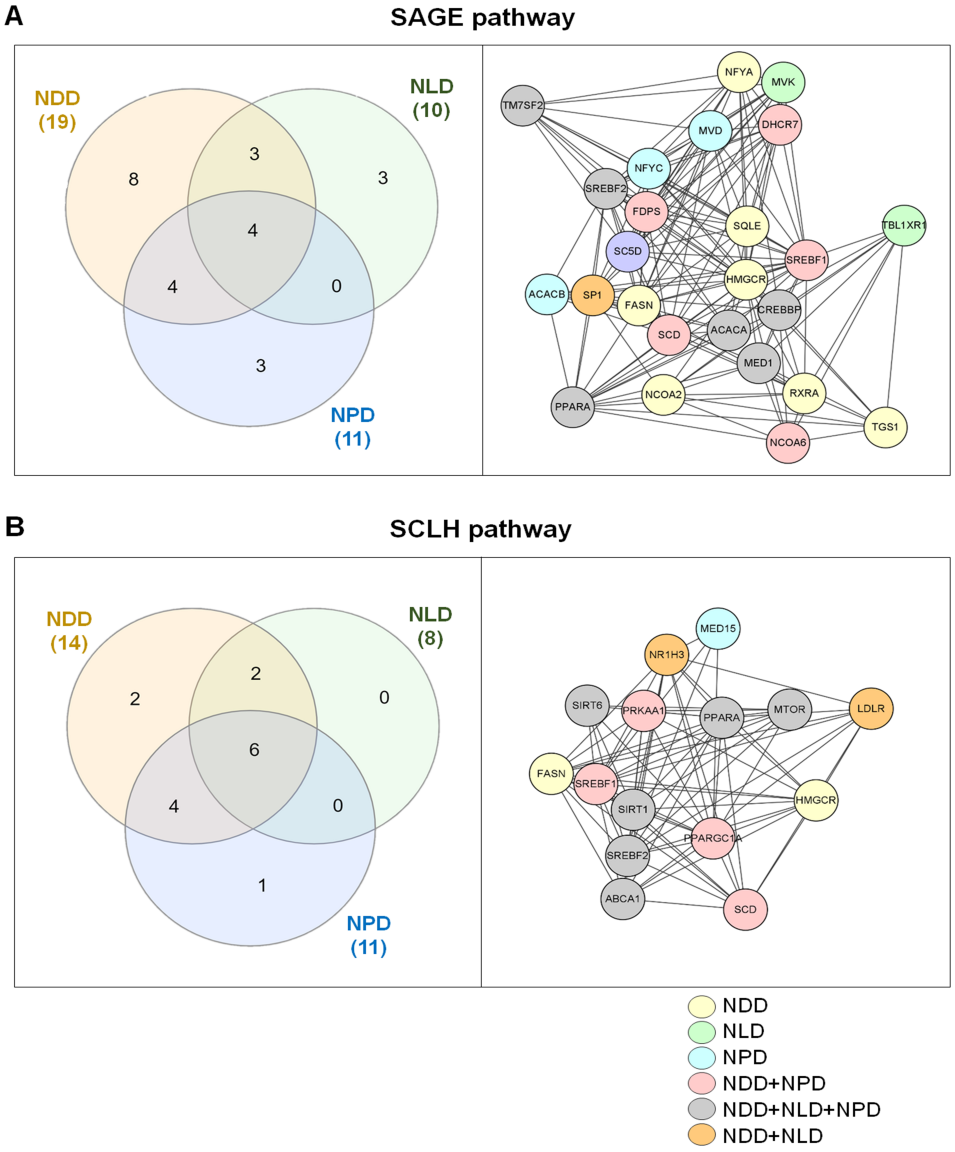

Fig. 3. Venn diagram and PPI networks of overlapping genes between the SREBP pathways and CNS disorders. Venn diagrams show the number of overlapping genes between two pathways related to SREBP (the SAGE and SCLH pathways) and common CNS disorders, (organized into NDDs, NLDs, and NPDs). A total of 25 and 15 genes were found to be in common between CNS disorders and the SAGE (A, left panel) and SCLH (B, left panel) pathways, respectively. PPI network constructs generated via STRING revealed genes that are specific for NDDs (yellow nodes), NLDs (green nodes), or NPDs (blue nodes) only; shared between two CNS disorder categories (pink or orange nodes); or shared among all (grey nodes) CNS disorder categories (A and B, right panels). PPI networks were generated with *Homo sapiens* as the species of interest, medium confidence of $\geq$0.400 for the minimum required interaction score, nodes corresponding to proteins, and edges representing protein-protein associations. Abbreviations: ABCA1, ATP binding cassette subfamily A member 1; ACACA, acetyl-CoA carboxylase alpha; ACACB, acetyl-CoA carboxylase beta; CREBBP, CREB binding protein; DHCR7, 7-dehydrocholesterol reductase; FASN, fatty acid synthase; FDPS, farnesyl diphosphate synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDLR, low density lipoprotein receptor; MED1, mevalonate diphosphate decarboxylase; MED15, mediator complex subunit 15; MTOR, mechanistic target of rapamycin kinase; MVD, mevalonate diphosphate decarboxylase; MVK, mevalonate kinase; NCOA2, nuclear receptor coactivator 2; NCOA6, nuclear receptor coactivator 6; NDDs, neurodegenerative diseases; NFYA, nuclear transcription factor Y subunit alpha; NFYC, nuclear transcription factor Y subunit gamma; NLDs, neurological diseases; NPDs, neuropsychiatric diseases; NR1H3, nuclear receptor subfamily 1 group H member 3; PPARA, peroxisome proliferator-activated receptor alpha; PPARGC1A, PPARG coactivator 1 alpha; PRKAA1, protein kinase AMP-activated catalytic subunit alpha 1; RXRA, retinoid X receptor alpha; SAGE, SREBP activation of gene expression; SCLH, SREBP cholesterol & lipid homeostasis pathway; SC5D, sterol-C5-desaturase; SCD, stearoyl-CoA desaturase; SIRT1, sirtuin 1; SIRT6, sirtuin 6; SP1, Sp1 transcription factor; SQLE, squalene epoxidase; SREBF1, sterol regulatory element binding transcription factor 1; SREBF2, sterol regulatory element binding transcription factor 2; TBL1XR1, TBL1X receptor 1; TGS1, trimethylguanosine synthase 1; TM7SF2, transmembrane 7 superfamily member 2.

Table 1. List of common genes between SREBP pathways and CNS-related disorders.

SREBP pathway	Activation of gene expression	Cholesterol & lipid homeostasis
NDD		
AD	*ACACA, CREBBP, FASN, FDPS, HMGCR, NCOA6, PPARA, RXRA, SCD, SP1, SQLE, SREBF2, TM7SF2*	*ABCA1, FASN, HMGCR, LDLR, MTOR, NR1H3, PPARA, PPARGC1A, PRKAA1, SCD, SIRT1, SIRT6, SREBF2*
HD	*CREBBP, RXRA, SP1, TM7SF2*	*ABCA1, MTOR, NR1H3, PPARGC1A, PRKAA1, SIRT1, SIRT6*
MS	*DHCR7, HMGCR, NCOA2, NFYA, PPARA, SP1*	*ABCA1, HMGCR, LDLR, MTOR, NR1H3, PPARA, PPARGC1A, SIRT1*
PD	*ACACA, FASN, MED1, PPARA, RXRA, SCD, SP1, SREBF1, TGS1, TM7SF2*	*ABCA1, FASN, LDLR, MTOR, PPARA, PPARGC1A, PRKAA1, SCD, SIRT1, SREBF1*
NLD		
Epilepsy	*CREBBP, MED1, PPARA, SC5D, SP1, TBL1XR1*	*ABCA1, MTOR, PPARA, SIRT1*
Ischemic stroke	*ACACA, MVK, PPARA, SREBF2, TM7SF2*	*ABCA1, LDLR, MTOR, NR1H3, PPARA, SIRT1, SIRT6, SREBF2*
NPD		
Anxiety	*ACACA, FDPS, MVD*	*PPARGC1A, SIRT1, SIRT6*
Bipolar disorder	*ACACA, NFYC, SCD, SREBF2*	*PPARGC1A, SCD, SIRT1, SREBF2*
Mental depression	*ACACA, ACACB, FDPS, MVD, PPARA, SCD, SREBF1*	*ABCA1, MTOR, PPARA, PPARGC1A, SCD, SIRT1, SIRT6, SREBF1*
PTSD	*PPARA*	*PPARA, SIRT1*
Schizophrenia	*ACACA, CREBBP, NCOA6, PPARA, SCD, SP1, SREBF1, SREBF2*	*ABCA1, MED15, MTOR, PPARA, PPARGC1A, PRKAA1, SCD, SIRT1, SREBF1, SREBF2*

ABCA1, ATP binding cassette subfamily A member 1; ACACA, acetyl-CoA carboxylase alpha; ACACB, acetyl-CoA carboxylase beta; AD, Alzheimer's disease; CREBBP, CREB binding protein; CNS, central nervous system; DHCR7, 7-dehydrocholesterol reductase; FASN, fatty acid synthase; FDPS, farnesyl diphosphate synthase; HD, Huntington's disease; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDLR, low density lipoprotein receptor; MED1, mevalonate diphosphate decarboxylase; MED15, mediator complex subunit 15; MS, multiple sclerosis; MTOR, mechanistic target of rapamycin kinase; MVD, mevalonate diphosphate decarboxylase; MVK, mevalonate kinase; NCOA2, nuclear receptor coactivator 2; NCOA6, nuclear receptor coactivator 6; NDDs, neurodegenerative diseases; NFYA, nuclear transcription factor Y subunit alpha; NFYC, nuclear transcription factor Y subunit gamma; NLDs, neurological diseases; NPDs, neuropsychiatric disease; NR1H3, nuclear receptor subfamily 1 group H member 3; PD, Parkinson's disease; PPARA, peroxisome proliferator-activated receptor alpha; PPARGC1A, PPARG coactivator 1 alpha; PRKAA1, protein kinase AMP-activated catalytic subunit alpha 1; PTSD, post-traumatic stress disorder; RXRA, retinoid X receptor alpha; SC5D, sterol-C5-desaturase; SCD, stearoyl-CoA desaturase; SIRT1, sirtuin 1; SIRT6, sirtuin 6; SP1, Sp1 transcription factor; SQLE, squalene epoxidase; SREBF1, sterol regulatory element binding transcription factor 1; SREBF2, sterol regulatory element binding transcription factor 2; SREBP, sterol regulatory binding protein; TBL1XR1, TBL1X receptor 1; TGS1, trimethylguanosine synthase 1; TM7SF2, transmembrane 7 superfamily member 2.

3.3 Functional and pathway enrichment analysis of gene products between SREBP pathway signaling genes associated with CNS disorders

Potential common mechanisms between SREBP pathway genes associated with CNS disorders were examined using GO and KEGG analyses. In the SAGE pathway, GO enrichment analysis resulted in 81 terms under the biological process category, 11 terms under the cellular component category, and 28 terms under the molecular function category. SAGE pathway-related GO enrichment analyses were mapped graphically using GOnet (Fig. 4). Only biological processes with a *p*-value threshold of $\leq 3.70 \times 10^{9}$, cellular component terms with a *p*-value threshold of $\leq 6.83 \times 10^{4}$, and molecular function terms with a *p*-value threshold of $\leq 3.46 \times 10^{5}$ were mapped for clarity. In the SCLH pathway, GO enrichment analysis identified 269 terms under the biological process category, 8 terms under the cellular component category, and 17 terms under the molecular function category. SCLH pathway-related GO enrichment analyses were also mapped graphically using GOnet (Fig. 5). Only biological processes with a *p*-value threshold of $\leq 5.27 \times 10^{7}$, cellular component terms with a *p*-value threshold of $\leq 3.72 \times 10^{4}$, and molecular function terms with a *p*-value threshold of $\leq 8.08 \times 10^{4}$ were mapped for clarity. GO enrichment components are indicated in different intensities of green, with higher intensities corresponding to a higher degree of correlation between the enrichment and gene involved. Gene colors are in turn specified based on their relative expression in the tissues of cerebral cortex (see legend). Fig. 6 shows the top enriched GO functional processes in bar graph format, with their corresponding *p*-values and corresponding number of genes associated for the SAGE and SCLH pathways. The most significantly enriched biological process was 'regulation of

Table 2. Percentages of common genes between SREBP pathways and CNS-related disorders.

SREBP pathway	Activation of gene expression	Cholesterol & lipid homeostasis
NDD		
AD	13 out of 3007 (0.43%)	13 out of 3007 (0.43%)
HD	4 out of 896 (0.45%)	7 out of 896 (0.78%)
MS	6 out of 1574 (0.38%)	8 out of 1574 (0.51%)
PD	10 out of 1846 (0.54%)	10 out of 1846 (0.54%)
NLD		
Epilepsy	6 out of 1111 (0.54%)	4 out of 1111 (0.36%)
Ischemic stroke	5 out of 1019 (0.49%)	8 out of 1019 (0.79%)
NPD		
Anxiety	3 out of 962 (0.31%)	3 out of 962 (0.31%)
Bipolar disorder	4 out of 1057 (0.38%)	4 out of 1057 (0.38%)
Mental depression	7 out of 1345 (0.52%)	8 out of 1345 (0.59%)
PTSD	1 out of 381 (0.26%)	2 out of 381 (0.52%)
Schizophrenia	8 out of 2524 (0.32%)	10 out of 2524 (0.40%)

AD, Alzheimer's disease; CNS, central nervous system; HD, Huntington's disease; MS, multiple sclerosis; NDD, neurodegenerative disease; NLD, neurological disease; NPD, neuropsychiatric disease; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; SREBP, sterol regulatory binding protein.

lipid metabolic process' for genes of both the SAGE and SCLH pathways, whereas the most significantly enriched molecular function was 'cis-regulatory region sequence-specific DNA binding'. The most significantly enriched cellular components were 'Acetyl-CoA carboxylase complex' for the SAGE pathway, and 'Acetyl-CoA carboxylase complex' and 'Fatty acid synthase complex' for the SCLH pathway. KEGG pathway analysis generated 15 pathways involved with SAGE pathway-related CNS disorder genes (Fig. 7A) and 16 pathways associated with SCLH pathway-related CNS disorder genes (Fig. 7B). Both the SAGE and SCLH pathways had 'AMP-activated protein kinase (AMPK) signaling pathway' as the most significant enriched term in KEGG analysis, which involved six and eight genes, respectively. The detailed list of genes and corresponding functional enrichment information is provided in **Supplementary Table 4**.

4. Discussion

In this study, using *in silico* bioinformatic analyses, we present evidence for the involvement of lipid deregulation in the signaling of most common CNS disorders. This is indicated by the presence of overlapping genes and biological pathways between common CNS disorders (NDDs, NLDs, and NPDs) and two pathways (SAGE and SCLH) of SREBP signaling.

4.1 SREBP signaling and enriched terms in the SAGE and SCLH pathways

The SAGE pathway is primarily involved in regulating the expression of genes encoding enzymes that are responsible for lipid homeostasis and control endogenous cholesterol, FA, and triacylglycerol levels, and phospholipid synthesis. There are three isoforms of SREBP: SREBP-1a, SREBP-1c, and SREBP-2. All isoforms have varying roles in lipid synthesis. SREBP-1c is primarily associated in FA synthesis and insulin-induced glucose metabolism (especially in lipogenesis), whereas SREBP-2 is implicated in cholesterol synthesis. In contrast, SREBP-1a seems to participate in both FA and cholesterol synthesis. SREBP transcription factors are generated from inactive precursors attached to the membranes of the ER. The precursor goes through a two-step cleavage process after activation to release the NH (2)-terminal active domain in the nucleus. The amount of cellular sterol influences SREBP processing. When sterol levels fall, the precursor is cleaved, allowing cholesterogenic genes to be activated and cholesterol homeostasis to be maintained. This sterol-sensitive mechanism appears to represent a primary point of regulation for the SREBP-1a and SREBP-2 isoforms, but not for SREBP-1c. Furthermore, insulin appears to be the primary regulator of SREBP-1c at the transcriptional level. The distinct regulatory and activation features of each SREBP isoform make it easier to coordinate lipid metabolism control [3,14,69].

The SCLH pathway, on the contrary, is a more specific subset of the SAGE pathway. It focuses on the cholesterol- and lipid-regulating activities of the SREBF2 isoform in conjunction with miR-33, a short noncoding RNA found inside the genes that code SREBPs. This microRNA inhibits the expression of the adenosine triphosphate-binding cassette transporter A1, a protein that controls the synthesis of high-density lipoprotein ("good" cholesterol) and aids in the removal of low-density lipoprotein ("bad" cholesterol) from the bloodstream [70]. Moreover, miR-33 regulates lipid homeostasis through the reduction of FA breakdown. This is accomplished through inhibition of the translation of numerous transcripts encoding proteins involved

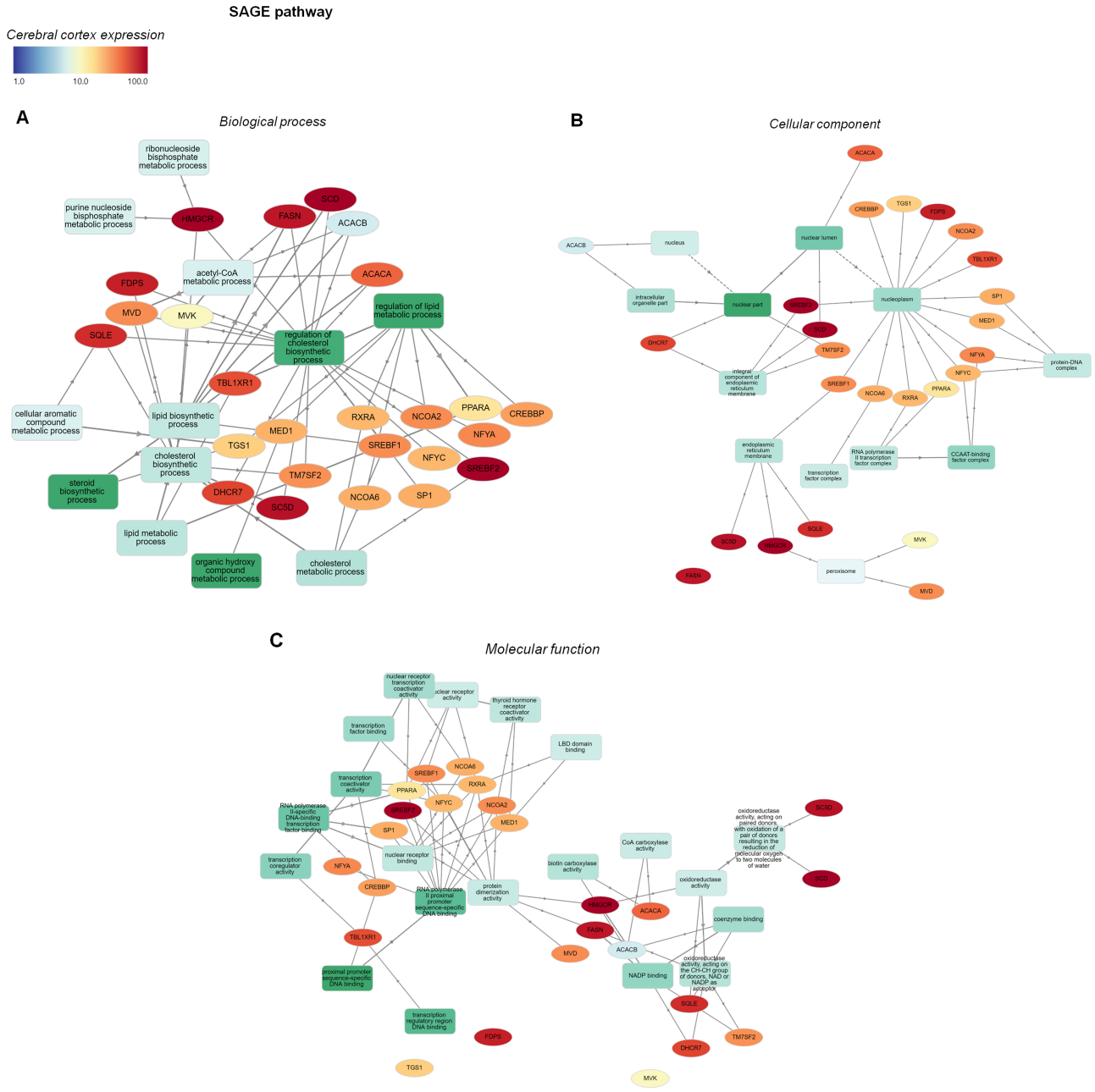

Fig. 4. GO functional enrichment analysis network of SAGE pathway genes overlapping with CNS disorder genes. GO enrichment analyses of SAGE pathway genes were mapped graphically using GOnet. Only biological processes (A) with a *p*-value threshold of $\leq 3.70 \times 10^{9}$, cellular component terms (B) with a *p*-value threshold of $\leq 6.83 \times 10^{4}$, and molecular function terms (C) with a *p*-value threshold of $\leq 3.46 \times 10^{5}$ were mapped for clarity. Enriched functional terms are presented as boxes with varying intensities of green, where higher intensities correspond to a higher degree of correlation between the enriched term and genes involved. Enriched genes are presented as oval nodes in a spectrum of blue to red, depending on their relative expression in the tissues of cerebral cortex (see legend). Abbreviations: ACACA, acetyl-CoA carboxylase alpha; ACACB, acetyl-CoA carboxylase beta; CREBBP, CREB binding protein; DHCR7, 7-dehydrocholesterol reductase; FASN, fatty acid synthase; FDPS, farnesyl diphosphate synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; MED1, mediator complex subunit 1; MVD, mevalonate diphosphate decarboxylase; MVK, mevalonate kinase; NCOA2, nuclear receptor coactivator 2; NCOA6, nuclear receptor coactivator 6; NFYA, nuclear transcription factor Y subunit alpha; NFYC, nuclear transcription factor Y subunit gamma; PPARA, peroxisome proliferator-activated receptor alpha; RXRA, retinoid X receptor alpha; SAGE, SREBP activation of gene expression; SCLH, SREBP cholesterol & lipid homeostasis pathway; SC5D, sterol-C5-desaturase; SCD, stearoyl-CoA desaturase; SP1, Sp1 transcription factor; SQLE, squalene epoxidase; SREBF1, sterol regulatory element binding transcription factor 1; SREBF2, sterol regulatory element binding transcription factor 2; TBL1XR1, TBL1X receptor 1; TGS1, trimethylguanosine synthase 1; TM7SF2, transmembrane 7 superfamily member 2.

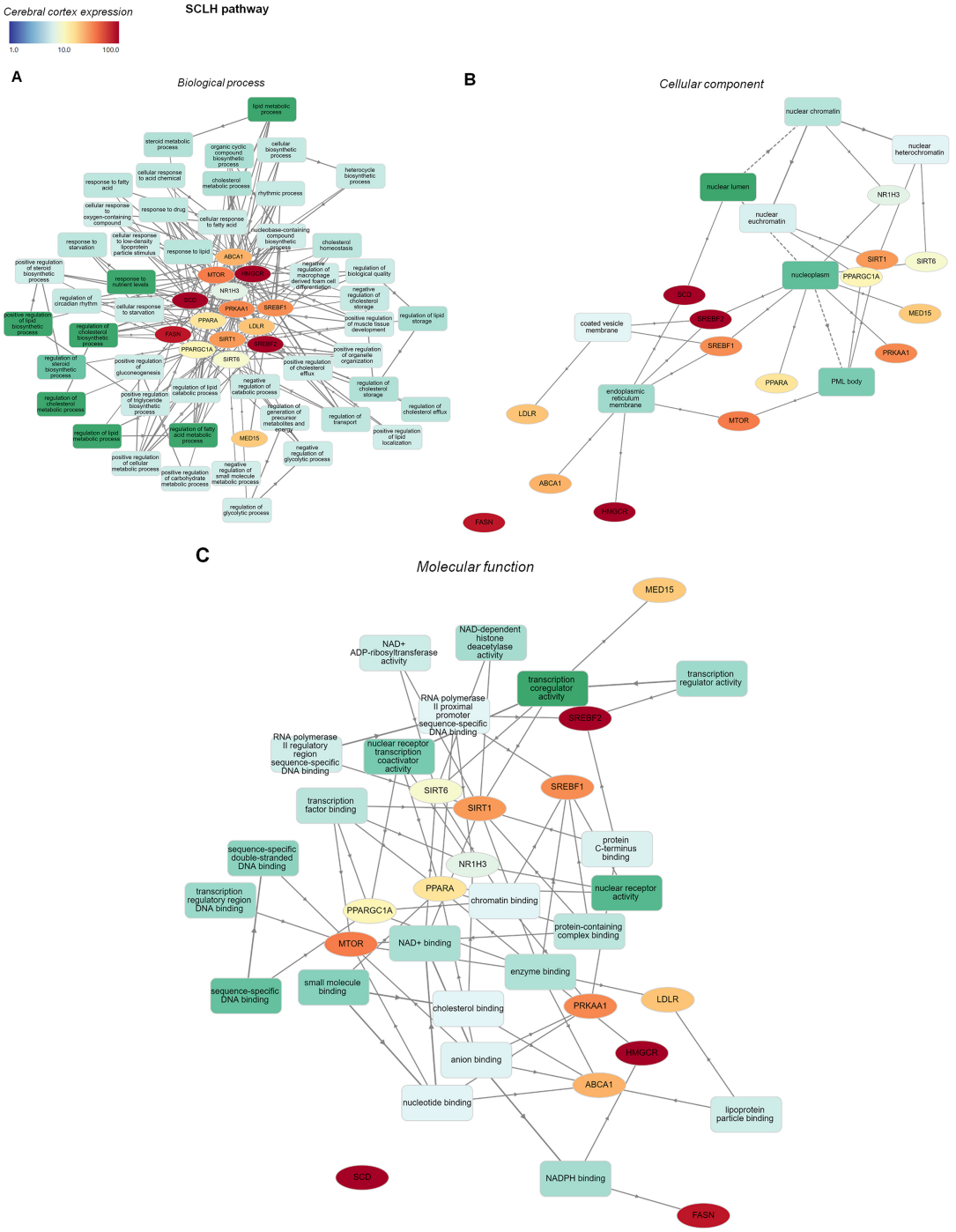

Fig. 5. GO functional enrichment analysis network of SCLH pathway genes overlapping with CNS disorder genes. GO enrichment analyses of SCLH pathway-related genes were mapped graphically using GOnet. Only biological processes (A) with a *p*-value threshold of $\leq 5.27 \times 10^{7}$, cellular component terms (B) with a *p*-value threshold of $\leq 3.72 \times 10^{4}$, and molecular function terms (C) with a *p*-value threshold of $\leq 8.08 \times 10^{4}$ were mapped for clarity. Enriched functional terms are presented as boxes with varying intensities of green, where higher intensities correspond to a higher degree of correlation between the enriched term and genes involved. Enriched genes are presented as oval nodes in a spectrum of blue to red, depending on their relative expression in the tissues of cerebral cortex (see legend). Abbreviations: ABCA1, ATP binding cassette subfamily A member 1; FASN, fatty acid synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDLR, low density lipoprotein receptor; MED15, mediator complex subunit 15; MTOR, mechanistic target of rapamycin kinase; NR1H3, nuclear receptor subfamily 1 group H member 3; PPARA, peroxisome proliferator-activated receptor alpha; PPARGC1A, PPARG coactivator 1 alpha; PRKAA1, protein kinase AMP-activated catalytic subunit alpha 1; SAGE, SREBP activation of gene expression; SCLH, SREBP cholesterol & lipid homeostasis pathway; SCD, stearoyl-CoA desaturase; SIRT1, sirtuin 1; SIRT6, sirtuin 6; SREBF1, sterol regulatory element binding transcription factor 1; SREBF2, sterol regulatory element binding transcription factor 2.

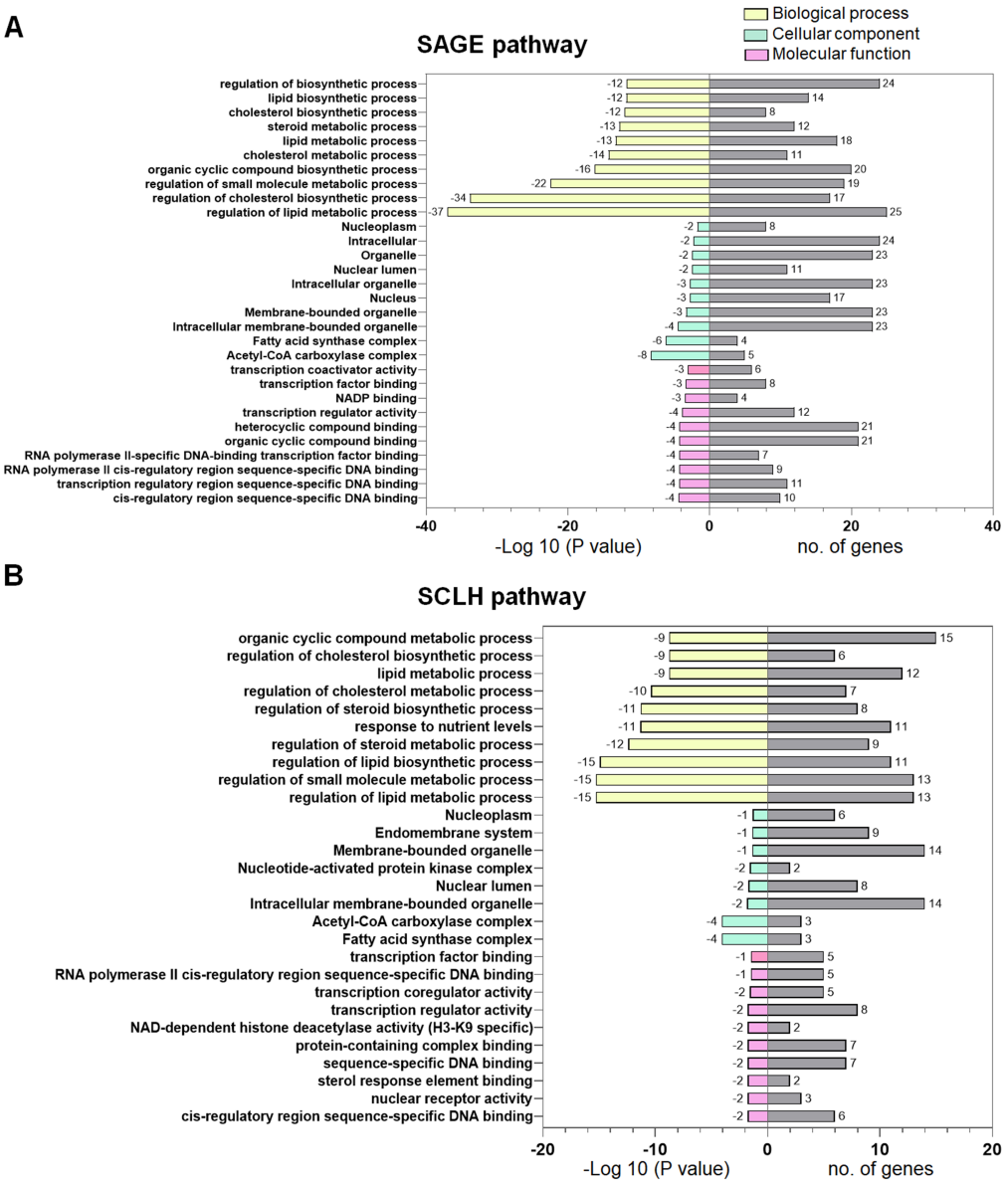

Fig. 6. Top biological functions of common genes between the SREBP pathways and CNS disorders, as analyzed by GO. Top enriched GO functional processes presented in bar graph format, with their corresponding *p*-values and corresponding number of genes associated for the SAGE (A) and SCLH (B) pathways. Yellow bars represent enriched biological processes, green bars represent enriched cellular components, and pink bars represent enriched molecular functions. Abbreviations: Acetyl-CoA, acetyl coenzyme A; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; SAGE, SREBP activation of gene expression; SCLH, SREBP cholesterol & lipid homeostasis pathway; SREBP, sterol regulatory element binding protein.

in FA oxidation, such as carnitine palmitoyltransferase 1A (CPT1A), hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta (HADHB), and carnitine O-octanoyltransferase (CROT) [71]. Despite sharing some common genes with the SAGE pathway, most of the genes involved in the SCLH pathway are unique. Thus, a separate analysis was deemed necessary for each pathway. Predictably, despite the separate analyses, functional enrichment results still elicited major congruencies in the results, with commonalities in the GO and KEGG functional enrichment analyses.

As expected, almost all the top enriched GO biological processes for both the SAGE and SCLH pathway-related genes included the regulation of lipid, cholesterol, and steroid metabolic and biosynthetic processes, as this is the well-established purpose of the SREBP pathway. The GO molecular functions also naturally involved transcription-related functions, including DNA, organic cyclic compound, and transcription factor binding, as SREBPs are, in fact, transcription factors. The top enriched GO subcellular compartments essentially mirrored the transcription-related molecular functions, with most of the enriched terms re-

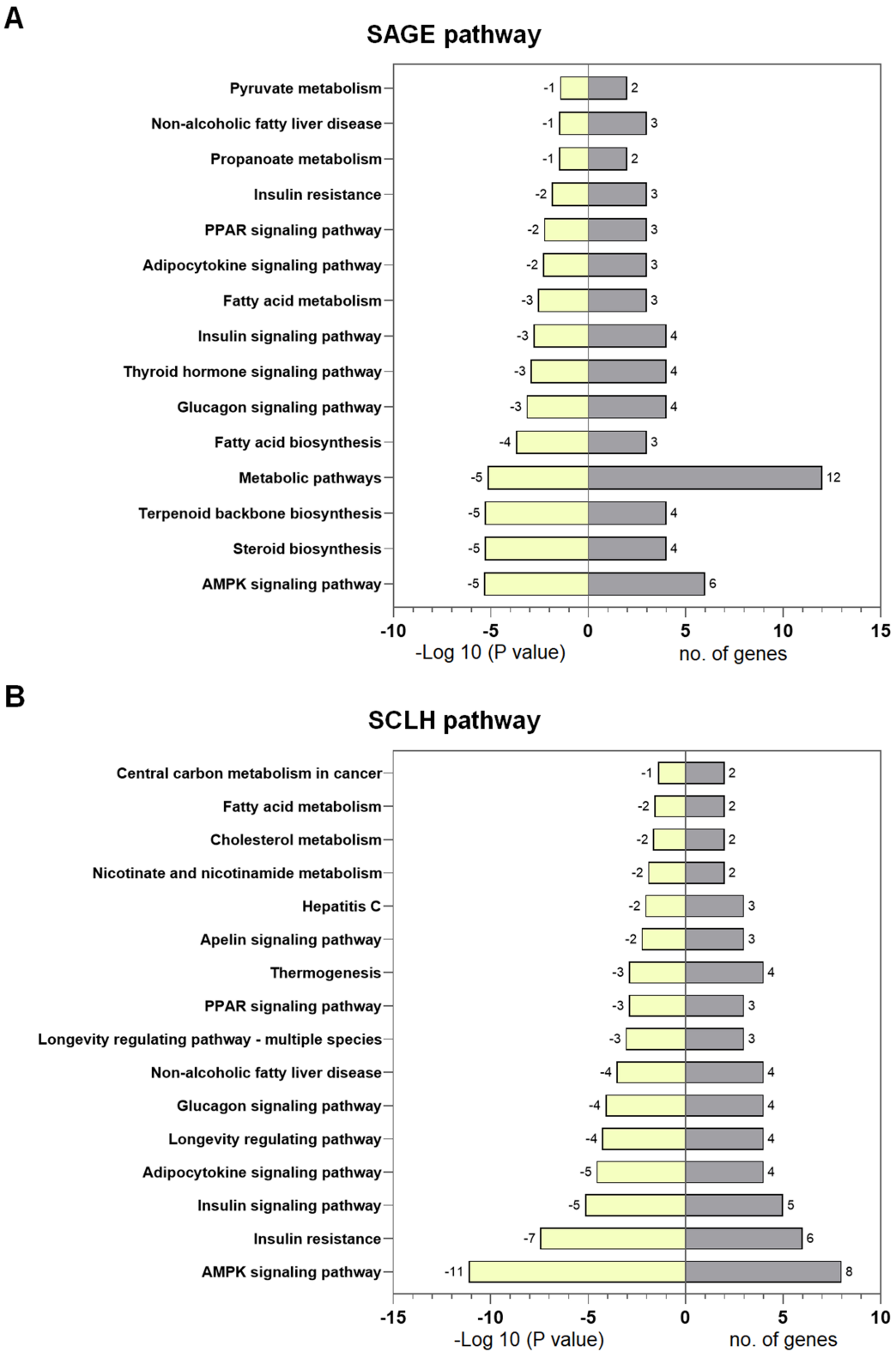

Fig. 7. Top enriched biological pathways between the SREBP pathways and CNS disorders, as analyzed by KEGG. Top enriched KEGG pathways presented in bar graph format, with their corresponding *p*-values and corresponding number of genes associated with the SAGE (A) and SCLH (B) pathways. Abbreviations: AMPK, AMP-activated protein kinase; PPAR, peroxisome proliferator-activated receptor; SAGE, SREBP activation of gene expression; SCLH, SREBP cholesterol & lipid homeostasis pathway; SREBP, sterol regulatory element binding protein.

flecting the nuclear compartment and its subparts, where transcription occurs. Moreover, the enzyme complexes for ACC and FASN were also among the top subcellular compartments enriched in SAGE pathway genes. Not surprisingly, KEGG analysis revealed AMPK signaling as the most significantly enriched pathway for both SAGE and SCLH pathway-related genes.

4.1.1 ACC and CNS disorders

ACC contributes significantly to the overall control of energy metabolism. ACC catalyzes the formation of malonyl-CoA, an essential substrate for FA synthesis in lipogenic tissues and a key regulatory molecule in muscle, brain, and other tissues. The specific activity of ACC is also rapidly modulated, being increased in response to insulin and decreased following exposure of cells to catabolic hormones or environmental stress. The acute control of ACC activity results from integrated changes in substrate supply, allosteric ligands, phosphorylation of multiple serine residues, and interactions with other proteins [72].

In CNS disorders, both the activation and inhibition of ACC play paradoxical roles in the action mechanisms of therapeutic candidates. In AD, some drug candidates primarily exert their therapeutic effects by inhibiting ACC. In animal models of AD, inhibition of ACC1 reduced cognitive decline and markers of aging via preservation of mitochondrial homeostasis in terms of increased levels of acetyl-CoA [73]. Further, reductions of beta-secretase activity and amyloid beta levels are induced by ACC inhibition in neuronal cells via the action of lipid homeostasis modulators, such as the pluripotent peptide leptin [74]. In Parkinson's disease, ACC1 is recruited and colocalized with a neurotoxic species of α-syn, the non-fibrillar phosphorylated α-synuclein aggregate. ACC1 phosphorylation indicates low ATP levels, AMPK activation, and oxidative stress, and induces mitochondrial fragmentation via reduced lipoylation, representing a therapeutic target for the disease [75]. In an animal model of cerebral ischemic stroke, ACC1 inhibition has also been presented as an underlying mechanism in calorie restriction-induced neuroprotection [76]. Likewise, the neuroprotective action of silibinin in an *in vitro* model of ischemic stroke requires the activation of ACC as a downstream target of the AMPK pathway [77]. In an animal model of mental depression, decreased levels of ACC and subsequent increased levels of malonyl-CoA in the hypothalamus were found to underlie the anorexic feeding behavior observed in socially defeated rats [78]. Conversely, increased ACC levels are also implicated in mouse models with depressive-like behavior induced by high-fat diet [79] and chronic mild food restriction [80]. Lastly, antipsychotic drugs against schizophrenia, such as clozapine, have been associated with elevated ACC1 levels, with possible roles in improving the myelin-synthesizing capabilities of oligodendrocytes [80] and activating the lipid regulatory system of neurons [81].

4.1.2 FASN and CNS disorders

In humans and birds, FASN plays a key role in *de novo* lipogenesis. FASN catalyzes all chemical steps in the conversion of acetyl-CoA and malonyl-CoA to palmitate using its seven active sites. Mitochondrial glycerol-3-phosphate acyltransferase (GPAT) catalyzes the first committed step in glycerophospholipid biosynthesis by acylating glycerol-3-phosphate with fatty acyl-CoA to produce 1-acyl-glycerol-3-phosphate (lysophosphatidic acid), which is acylated to create triacylglycerol for storage. Allosteric effectors or covalent modification are not known to regulate FASN activity. FASN concentration, however, is extremely sensitive to nutritional, hormonal, and developmental status; when animals are subjected to different nutritional and hormonal manipulations, the concentration or activity of FASN in lipogenic tissues, such as liver and adipose tissues, changes dramatically [82–84].

In NDDs, FASN activity has been implicated as a target for therapeutics. A FAS inhibitor successfully alleviated cognitive loss, modulated lipid metabolism, and reduced inflammation and lipid peroxidation in the brains of transgenic AD mouse models [85]. In genetic models of PD, such as flies, mouse cells, patient-derived fibroblasts, and induced pluripotent stem cell-derived dopaminergic neurons, partial genetic and pharmacological inhibition of FASN decreases toxicity generated by PINK1 deficiency [86]. This is corroborated by studies reporting that the level of α-synuclein toxicity is correlated with FASN activity and intracellular redox status, with cells becoming more resistant to α-synuclein when they are unable to store neutral lipids [87].

4.2 AMPK signaling in SAGE and SCLH genes related to CNS disorders

The top enriched pathway for both SAGE and SCLH genes related with CNS disorders is the AMPK signaling pathway. This is not surprising because the top enriched subcellular compartments were ACC and FASN, enzymes that are both known to be regulated by AMPK as its downstream targets. Both ACC and FASN are mainly inhibited by the phosphorylation of AMPK. ACC inhibition by AMPK is generally coupled with thrombus formation [88], hypolipogenic pathways in the liver [89], and the insulin-sensitizing effect of metformin action [90]. FASN inhibition by AMPK is also implicated in cancer [91,92] and tumor suppression [93].

AMPK pathway genes associated with the SAGE pathway included *HMGCR*, *FASN*, *ACACB*, *SREBF1*, *SCD*, and *ACACA*, whereas those related to the SCLH pathway comprised *SIRT1*, *PPARGC1A*, *HMGCR*, *FASN*, *PRKAA1*, *SREBF1*, *MTOR*, and *SCD*. AMPK is a serine/threonine kinase found in several tissues, and it serves as a major energy sensor. It is a heterotrimeric complex made up of a catalytic component and regulatory subunits [94]. The AMPK signaling pathway boosts ATP-producing pathways whilst

inhibiting ATP-consuming pathways. Several factors, including low glucose, hypoxia, ischemia, and heat shock, can activate the kinase [95].

The modulation of lipid metabolism is one of the most well-known functions of AMPK; it promotes FA oxidation whilst inhibiting FA synthesis. AMPK phosphorylation inhibits ACC synthesis and lowers malonyl-CoA levels. Malonyl-CoA is an FA elongation and *de novo* synthesis substrate [96]. AMPK is also a carnitine palmitoyl transferase I inhibitor, which is essential for the transfer of primed cytosolic FAs into the mitochondrion for degradative beta-oxidation [97]. This kinase has long been a therapeutic target for metabolic disorders and malignancies. In particular, the involvement of aberrant AMPK pathway activity in CNS illnesses and diseases is well documented, with particular focus on the clinical repercussions of the pathway and its role as a therapeutic target [98–100].

4.2.1 AMPK signaling in NDDs

Several review papers have elucidated the connection of the AMPK pathway with NDDs [98,101,102]. In AD, the AMPK pathway predominantly confers deleterious roles in the late stages of the disease [102]. Excitotoxicity, as well as metabolic and oxidative stress, are all hallmarks of AD [103,104]. Mitochondrial failure eventually results in the generation of reactive oxygen species and a rise in the AMP/ATP ratio, which are correlated to oxidative and metabolic stressors, respectively [105]. These two events activate AMPK, which reduces protein synthesis and contributes to memory loss by causing synaptic loss and deficiency of long-term potentiation [106,107]. AMPK is also involved in tau and amyloid protein modulation. AMPK phosphorylates tau protein, modifying microtubule assembly and, as a result, vesicle, and mitochondria axonal transit [108]. In addition, AMPK is involved in the generation and degradation of amyloid-β peptides. Finally, amyloid-β and tau may play a role in prolonged AMPK activation by causing mitochondrial dysfunction and excitotoxicity [109]. In PD, AMPK signaling plays a dual role. Mitochondrial changes are caused by a combination of environmental and genetic causes. These changes eventually result in oxidative and metabolic stress [110]. These stressors activate AMPK, which then phosphorylates α-synuclein, causing it to aggregate and eventually cause neurodegeneration [75]. In addition, reduced protein synthesis induced by AMPK activation could also cause neurodegeneration [111]. However, AMPK may also exert a neuroprotective effect by stimulating the destruction of damaged mitochondria and α-synuclein aggregates through autophagy [112,113]. In HD, AMPK activation plays a detrimental role. Mutant huntingtin causes oxidative stress and hypo-metabolism in mitochondrial cells [114,115]. This helps activate AMPK and transfer it from the cytoplasm to the nucleus, where it suppresses the anti-apoptotic protein Bcl2. This mechanism encourages apoptosis, which leads to neurodegeneration [116,117].

Collectively, the role of AMPK in NDDs may be viewed as a double-edged sword [102]. During the early stages of NDDs, the activation of AMPK may be beneficial, as it may help restore energy homeostasis and eliminate protein aggregates that can be harmful to neurons [99]. Nevertheless, chronic AMPK activation is detrimental to neurons in late-stage diseases. Moreover, AMPK overactivation may cause neurodegeneration via various signaling mechanisms. Reduction of protein synthesis may lead to synaptic loss and decreased synaptic plasticity, eventually leading to neurodegeneration. Finally, increased autophagosome synthesis coupled with deregulated lysosomal clearance (known to occur in these disorders) leads to an increase in hazardous proteins aggregates and mitochondrial defects [100,118,119].

4.2.2 AMPK signaling in NLDs

In NLDs such as epilepsy and ischemic stroke, most evidence points to beneficial effects of AMPK pathway activation, leading to neuroprotection. In epilepsy, the action mechanism of several anti-epileptic drug candidates has been attributed to the activation of the AMPK pathway. The neuroprotective effects of AMPK phosphorylation via amelioration of oxidative stress through reduction of reactive oxygen species and malondialdehyde, as well as strengthening of glutathione peroxidase and superoxide dismutase, were associated with the epilepsy-attenuating properties of β-hydroxybutyric acid (BHBA) in C57BL/6 J mice exposed to lithium chloride and pilocarpine [120]. Further, the therapeutic potential of metformin against epilepsy has been attributed to AMPK activation. Metformin has been reported to control seizure attacks by attenuating seizure generation, delaying the onset of epilepsy, reducing hippocampal neuronal loss, and averting cognitive impairments in both acute and chronic models of epileptic seizures [121,122]. Activation of the AMPK/PPARα pathway was also associated in the alleviation of epileptic symptoms in lithium-pilocarpine treated Sprague-Dawley rats [123]. Additionally, increased AMPK signaling has been implicated in the ability of calorie-restricted diet to reduce seizures in people with epilepsy [124]. In ischemic stroke, numerous studies have revealed the protective role of AMPK and its possible use as a potent drug candidate [110,125]. A peptide version of adiponectin, a fat-derived hormone, was able to decrease cerebral infarction volume, alleviate brain edema, improve neurological function, and exert antioxidant, anti-inflammatory, and antiapoptotic effects against cerebral ischemia-reperfusion injury in C57BL/6J mouse models of transient middle cerebral artery occlusion, through the upregulation of AMPK and glycogen synthase kinase-3β phosphorylation [126]. Furthermore, C1q/tumor necrosis factor-related protein-3 has been shown to prevent mitochondrial oxygen-glucose deprivation/reoxygenation injury in hippocampal neuronal cells by activating the AMPK/SIRT1-PGC-1α pathway [127].

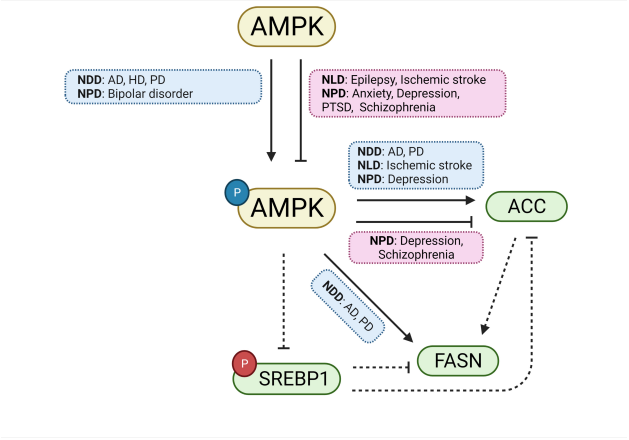

Fig. 8. ACC, FASN, and AMPK are involved in the genetic overlap between SREBP and CNS disorders. A schematic diagram summarizing the pathways governing ACC, FASN, and AMPK, and their involvement in CNS disorders. Both the activation and inhibition of AMPK are involved in the mechanisms underlying several CNS disorders. Likewise, both the activation and inhibition of the ACC enzyme are involved in CNS disorders. For FASN, only its activation is implicated in CNS disorders. Boxes in blue indicate involvement with CNS disorders during activation, whereas red boxes indicate involvement with disorders during inhibition. Inhibitory phosphorylations are shown in red and activating phosphorylations are shown in blue. Solid lines are evidenced by studies included in the current study; broken lines represent possible pathways not directly implicated by the reports included in the current study. Abbreviations: ACC, acetyl-CoA carboxylase; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; FASN, fatty acid synthase; HD, Huntington's disease; NDDs, neurodegenerative diseases; NLDs, neurological diseases; NPDs, neuropsychiatric diseases PD, Parkinson's disease; PTSD, post-traumatic stress disorder; SREBP, sterol regulatory element binding protein.

4.2.3 AMPK signaling in NPDs

The involvement of the AMPK pathway in NPDs is also well-reported. AMPK signaling plays a dual role in NPDs, in which both beneficial and deleterious involvements have been documented. In anxiety, decreased levels of phosphorylated AMPK are associated with anxiety, decreasing synaptic protein levels in the cortex of mice subjected to unpredictable chronic mild stress. This suggests that AMPK inactivation may be a mechanism by which unpredictable chronic mild stress induces anxiety [128]. In bipolar disorder, AMPK upregulation is associated with the manic phase of the disorder, which is characterized by increased mitochondrial respiration and ATP production [129]. In mental depression, antidepressant drugs exert their therapeutic effects via increased phosphorylation of AMPK. In a mouse model of inflammatory bowel disease, liver hydrolysate prevented depressive-like behavior by enhancing hippocampal neurogenesis through the AMPK/brain-derived neurotrophic factor (BDNF) pathway and anti-neuroinflammation in the hippocampus [130]. Moreover, the ability of metformin to produce antidepressant effects is credited to the upregulation of BDNF via activation of AMPK and cAMP-response element binding protein [131]. In PTSD, increased AMPK activity was associated with the ability of electroacupuncture to improve hippocampal neurogenesis and ameliorate anxiety-like behavior in an enhanced single prolonged stress model of PTSD in rats [132]. In schizophrenia, common differentially methylated genes were found to be significantly involved in the AMPK signaling pathways [133]. AMPK expression was also reported to be altered in the cortical excitatory neurons of patients with mutations in the disrupted schizophrenia 1 (*DISC1*) gene [134]. The deletion of 10 genes in human 1q21.1, a genetic risk of schizophrenia, also involves the β-subunit of the AMPK complex. Lastly, the action of antipsychotics against schizophrenia and their concurrent metabolic side effects are also underlaid by the activity of AMPK [135,136] and its downstream pathway SREBP [137]. The participation of SREBP signaling in schizophrenia is corroborated by our studies implicating the involvement of SREBP-1c in the maintenance of hippocampal neuroarchitecture and function. Mice with SREBP-1c deficiency exhibited schizophrenia-like behavior [52], impaired hippocampal dendritic neuroarchitecture [54], and altered transcriptomic data related to maintenance of normal hippocampal function [53].

4.3 Involvement of ACC, FASN, and AMPK in the genetic overlap between SREBP and CNS disorders

In summary, we identified commonly expressed genes, biological processes, molecular functions, subcellular compartments, and biological pathways between the SREBP pathways and common CNS disorders. GO biological process and molecular function analyses confirmed the lipid regulatory action of the genes, as well as their transcription-related functions, all of which agree with the primary characteristic and main mandate of the SREBP pathways. Interestingly, most of the common genes were part of the subcellular compartments of either or both ACC and FASN enzymes, which play a key role in the regulation of energy metabolism and possibly serve as downstream targets of AMPK. Unsurprisingly, the top enriched pathway of the overlapping genes was the AMPK signaling pathway. We identified *ACACA*, *ACACB*, *FASN*, *HMGCR*, *MTOR*, *PPARGC1A*, *PRKAA1*, *SCD*, *SIRT1*, and *SREBF1* as the top genes significantly enriched under this pathway. Both animal models and clinical studies consistently showed the role of AMPK signaling in mediating the involvement of the SREBP pathway in the lipid deregulation-related mechanisms underlying NDDs, NLDs, and NPDs. However, the relevance of gene-environment interaction is another noteworthy factor that may affect disease outcome, and thus cannot be discounted.

4.4 Future studies

Further studies involving a more systematic literature review of the specific roles of each implicated common gene may shed more light in the treatment and diagnostic procedures currently available for CNS disorders. Likewise, gain- or loss-of-function experiments involving the same genes may provide an insight to which new models can be generated, replicating the lipid deregulated pathways of CNS disorders. Finally, investigation of other pathways related to lipid metabolism other than the SREBP signaling pathway may also uncover novel mechanisms underlying CNS disorders.

5. Conclusions

The elucidation of the importance of lipids in neuroscience is evolving with the advent of techniques allowing for a more detailed analysis of the types and roles of lipids in the nervous system. Several studies have already suggested the involvement of lipid homeostasis in the mechanism of CNS disorders. SREBP signaling is a transcriptomic pathway regulating lipid homeostasis, frequently implicated with organs that store or process large amounts of lipids, such as the liver and adipose tissue. The brain, which predominantly consists of lipids, is also affected by SREBP signaling. This is evidenced by the commonality between the genetic components of the pathway and the genes involved in NDDs, NLDs, and NPDs. *In silico* bioinformatic analysis revealed that the enzymes ACC and FASN, as well as the AMPK signaling pathway, are indisputably involved in the mechanism of disease progression and/or resolution in the CNS (Fig. 8). Lastly, lipid dysregulation-related animal models of NDDs, NLDs, and NPDs may present a new avenue by which research discovering novel, safe, and effective therapeutics may be propelled.

Abbreviations

ABCA1, ATP binding cassette subfamily A member 1; ACACA, acetyl-CoA carboxylase alpha; ACACB, acetyl-CoA carboxylase beta; ACC, acetyl-CoA carboxylase; Acetyl-CoA, acetyl coenzyme A; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; bHLH-LZ, basic helix-loop-helix leucine zipper; CNS, central nervous system; CREBBP, CREB binding protein; DAVID, Database for Annotation, Visualization and Integrated Discovery; DHCR7, 7-dehydrocholesterol reductase; ER, endoplasmic reticulum; FASN, fatty acid synthase; FDPS, farnesyl diphosphate synthase; FunRich, Functional Enrichment analysis tool; Gly, glycine; GO, Gene Ontology; GSEA, Gene Set Enrichment Analysis; HD, Huntington's disease; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; KEGG, Kyoto Encyclopedia of Genes and Genomes; LDLR, low density lipoprotein receptor; MED1, mevalonate diphosphate decarboxylase; MED15, mediator complex subunit 15; MTOR, mechanistic target of rapamycin kinase; MVD, mevalonate diphosphate decarboxylase; MVK, mevalonate kinase; NADP, nicotinamide adenine dinucleotide phosphate; NCOA2, nuclear receptor coactivator 2; NCOA6, nuclear receptor coactivator 6; NDDs, neurodegenerative diseases; NFYA, nuclear transcription factor Y subunit alpha; NFYC, nuclear transcription factor Y subunit gamma; NLDs, neurological diseases; NPDs, neuropsychiatric diseases; NR1H3, nuclear receptor subfamily 1 group H member 3; MSigDB, Molecular Signatures Database; PD, Parkinson's disease; PPARA, peroxisome proliferator-activated receptor alpha; PPARGC1A, PPARG coactivator 1 alpha; PPI, protein-protein interaction; PRKAA1, protein kinase AMP-activated catalytic subunit alpha 1; Pro, proline; PTSD, post-traumatic stress disorder; RXRA, retinoid X receptor alpha; SAGE, SREBP activation of gene expression; SCLH, SREBP cholesterol & lipid homeostasis pathway; SC5D, sterol-C5-desaturase; SCD, stearoyl-CoA desaturase; Ser, serine; SIRT1, sirtuin 1; SIRT6, sirtuin 6; SP1, Sp1 transcription factor; SQLE, squalene epoxidase; SREBF1, sterol regulatory element binding transcription factor 1; SREBF2, sterol regulatory element binding transcription factor 2; SREBP, sterol regulatory element binding protein; STRING, Search Tool for Retrieval of Interacting Genes; TA, transactivation; TBL1XR1, TBL1X receptor 1; TGS1, trimethylguanosine synthase 1; TM7SF2, transmembrane 7 superfamily member 2.

Author contributions

MJA and CM conceived and designed the experiments; MJA designed the methodology; MJA did the formal analysis; MJA wrote the original draft; CM edited and reviewed the draft; CM supervised the study, CM was responsible for funding acquisition.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

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Conflict of interest

The authors declare no conflict of interest. CM is serving as one of the Editorial Board members of this journal. We declare that CM had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to UGP and RF.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2103095.

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