Current Neuropharmacology, 2022, *20,* 1564-1578

REVIEW ARTICLE

Targeting PI3K by Natural Products: A Potential Therapeutic Strategy for Attention-deficit Hyperactivity Disorder

Tayebeh Noori[1], Mousa Sahebgharani[2], Antoni Sureda[3,4], Eduardo Sobarzo-Sanchez[5,6], Sajad Fakhri[1] and Samira Shirooie[1,*]

[1]*Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran;* [2]*Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran;* [3]*Research Group on Community Nutrition and Oxidative Stress (NUCOX) and Health Research Institute of Balearic Islands (IdISBa), University of Balearic Islands-IUNICS, Palma de Mallorca E-07122, Balearic Islands, Spain;* [4]*CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain;* [5]*Instituto de Investigación y Postgrado, Facultad de Ciencias de la Salud, Universidad Central de Chile, Chile;* [6]*Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago, Spain*

ARTICLE HISTORY

Received: July 21, 2021
Revised: January 02, 2022
Accepted: January 12, 2022

DOI:
10.2174/1570159X20666220119125040

Abstract: Attention-Deficit Hyperactivity Disorder (ADHD) is a highly prevalent childhood psychiatric disorder. In general, a child with ADHD has significant attention problems with difficulty concentrating on a subject and is generally associated with impulsivity and excessive activity. The etiology of ADHD in most patients is unknown, although it is considered to be a multifactorial disease caused by a combination of genetics and environmental factors. Diverse factors, such as the existence of mental, nutritional, or general health problems during childhood, as well as smoking and alcohol drinking during pregnancy, are related to an increased risk of ADHD. Behavioral and psychological characteristics of ADHD include anxiety, mood disorders, behavioral disorders, language disorders, and learning disabilities. These symptoms affect individuals, families, and communities, negatively altering educational and social results, strained parent-child relationships, and increased use of health services. ADHD may be associated with deficits in inhibitory frontostriatal noradrenergic neurons on lower striatal structures that are predominantly driven by dopaminergic neurons. Phosphoinositide 3-kinases (PI3Ks) are a conserved family of lipid kinases that control a number of cellular processes, including cell proliferation, differentiation, migration, insulin metabolism, and apoptosis. Since PI3K plays an important role in controlling the noradrenergic neuron, it opens up new insights into research on ADHD and other developmental brain diseases. This review presents evidence for the potential usefulness of PI3K and its modulators as a potential treatment for ADHD.

Keywords: Attention-deficit hyperactivity disorder (ADHD), Phosphoinositide 3-kinases (PI3Ks), neurogenesis, dopamine, etiology, natural products.

1. INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral disorder characterized by inattentiveness and/or hyperactivity/impulsivity [1]. This disorder affects about 8%–12% of children worldwide, and up to 65% continue to have signs of ADHD and neuropsychological impairments in adulthood [2]. The prevalence of ADHD is higher in boys than in girls, although increasingly more girls are being diagnosed [3]. According to the severity of symptoms, ADHD can be categorized into 3 subtypes: predominantly inattentive, predominantly hyperactive-impulsive, and a combination of both [4]. Many children with ADHD have significant functional impairments compared to children without ADHD, for example, deficits in working memory and poor ability to maintain attention [1]. Anxiety, conduct/opposition disorders, learning and language disabilities are among the behavioral and psychological symptoms of ADHD [5]. These problems can make difficult the diagnosis and treatment of ADHD. These ADHD symptoms negatively affect many aspects of individuals, families, and society, such as educational and social outcomes, parent-child relationships, and increased use of healthcare services [6, 7]. ADHD usually occurs alongside other disorders, for instance, oppositional defiant disorder (ODD), conduct disorder (CD), and anxiety disorder [8]. It has also been shown that another cause of ADHD is mitochondrial dysfunction (MD). It has been suggested that MD is the most likely mechanism by which oxidative stress (OS) contributes to the pathogenesis of ADHD [9]. In addition, various studies showed a relationship between dysregulation in the neurotransmission of dopamine, norepinephrine, glutamate, and

*Address correspondence to this author at the Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran. E-mail: shirooie@gmail.com

1875-6190/22 $65.00+.00

serotonin systems with ADHD symptoms [10-12]. The goals of ADHD therapy focus on reducing ADHD symptoms, improving performance and social functioning, and quality of life [13, 14]. There are pharmacological and non-pharmacological approaches for the management of ADHD. The non-pharmacological options, such as behavioral therapies, social skills, dietary and nutritional treatments (elimination of sugar, colorants, or preservatives), and aerobic exercise and yoga are less effective than pharmacologic therapy [15]. The most effective treatment for the core ADHD symptoms are stimulants (including dextroamphetamine, lisdexamfetamine, methylphenidate, mixed salts amphetamine), modafinil, atomoxetine, alpha2 -adrenergic agonists (such as clonidine and guanfacine), antidepressants (bupropion and venlafaxine), antipsychotics (risperidone), and natural products (including chamomile, valerian, melatonin, omega-3 polyunsaturated fatty acids, B vitamins, evening primrose oil and ginkgo biloba) [13].

Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes with a significant role in many metabolic processes that control numerous aspects of cell physiology. PI3Ks are evolutionarily preserved enzymes that transduce signals of mitogenic and metabolic origin to promote cell growth, proliferation, migration, and apoptosis [16]. In addition, PI3K signaling is involved in regulating the action of psychomotor stimulants, such as amphetamines (AMPH) *via* dopamine transporter (DAT) membrane expression [17]. Noradrenergic (NA) neurons of the locus coeruleus (LC) that constitute the central source of noradrenaline in the brain are rich in $PI3K_{\gamma}$ isoform and are involved in behavioral flexibility and attention [18, 19]. For this reason, $PI3K_{\gamma}$ is a target in the search for ADHD molecular bases. This signaling enzyme has a vital role in various metabolic processes and has been frequently explored in the context of immune and cardiovascular performances [20]. Although $PI3K_{\gamma}$ has hardly been studied in the brain, one report proposed a role for this kinase in regulating behavioral flexibility involving the N-methyl-D-aspartate (NMDA) receptor during a long period of depression [21]. Moreover, PI3K is involved in the regulation of the cAMP-responsive element-binding protein (CREB) pathway and the A2A receptor (ADORA2A) gene, which is linked to the dopamine neurotransmitter system and the regulation of alertness, suggesting a potential association with ADHD traits [22, 23]. This review attempts to compile the information available on the possible therapeutic utility of PI3K and some of its natural and synthetic modulators, such as Oxymatrine (OMT), Notoginsenoside R1 (NGR1), Epigalocatechin-3-gallate (EGCG), Taxifolin, and FTY720 (a sphingosine-1-phosphate receptor modulator) in the treatment of ADHD.

2. ADHD AND ITS ETIOLOGY

Although ADHD has been extensively studied, its etiology is not well understood. A greater risk of developing ADHD is related to a complex interplay between hereditary and nonhereditary agents [24].

2.1. Genetics and Epigenetic Factors

ADHD is a heterogeneous disorder in which genetics and environment are involved in its development. Genetic factors play a significant role in the etiology of ADHD, as it was demonstrated by analyzing the family transmission of ADHD and in twin and adoption studies, reporting an inheritance of ADHD of around 75% [25-27]. Candidates for risk genes for ADHD include genes that participate in regulating neurotransmitter pathways, such as dopamine, norepinephrine, and serotonin [26, 28]. In fact, most studies have focused on genes involved in dopamine [29] and serotonin transporters [30], and catechol-*O*-methyl transferase (COMT) [31]. Moreover, all these genes are also involved in signal transduction at the neuronal synapse. The relationship between the synaptic dysfunction of DAT and ADHD suggests the therapeutic utility of DAT-interacting psychostimulants, such as methylphenidate [32]. Studies have shown that the gut microbiome affects dopamine levels in the frontal cortex and striatum in rodents (two areas of the brain that influence executive function) as well as serotonin, noradrenaline, gamma-aminobutyric acid, and other neurotransmitters and their precursors [33-35]. Age-related alterations in dopaminergic activity are affected by the change in dopamine transporter (DAT) expression related to elevated striatum DAT expression in ADHD [36]. Another important pathway involved in ADHD is the Wnt/catenin-signaling pathway associated with cell differentiation and proliferation [37]. Aebi *et al.* indicated a significant enrichment of Wnt/β-catenin signaling in ADHD through bioinformatics clustering of the genome-wide association studies (GWAS) data [38].

By identifying a set of genes that affect neurotransmitters in the brain [39], it has been shown that rare copy number variants or accumulations of larger deletions and duplications may be important for ADHD etiology [40]. Molecular genetic findings are developing rapidly [41] and among them stands out the strong overlap with the genetics of ADHD-related traits and other health risk behaviors in the population [42].

2.2. Prematurity/Low Birth Weight

Due to the evolutionary nature of ADHD, much research has focused on early life risk factors that may cause neurodevelopmental side effects and signs of ADHD, with low birth weight (LBW) being one of the strongest risk factors for ADHD [43]. Premature infants (less than 26 weeks) are about 4 times more susceptible to developing ADHD, especially the inattentive subgroup, while premature infants over 26 weeks are twice as likely as full-term babies [24, 44]. Among preterm infants with very LWB, accounting for almost 2% of all live births and, despite an 85% improvement in survival, half of them have cognitive and neurodevelopmental disabilities. In fact, very LBW children present a higher risk of white matter injury, which is related to cognitive and motor health impairments [45]. Delays in development and cognitive acquisition are more evident in LBW than those of average weight during childhood [46].

2.3. Environmental Factors

Environmental factors are among the elements that influence the development of ADHD and, 20-30% of ADHD is suggested to be related to these factors [47]. Contact with environmental toxins, chemicals, and heavy metals, such as lead and mercury, organochlorine and organophosphate pesticides, and phthalates, as well as nutritional and lifestyle / psychosocial elements, are environmental risk factors for ADHD [48-52]. Also, it has been reported that chronic expo-

sure to alcohol and/or tobacco smoke (during pregnancy) are also relevant environmental risk factors for ADHD [53].

2.4. Diet

There is evidence that different dietary factors, mainly deficiencies in certain nutrients or following an unhealthy diet, are related to childhood behavior disorders, such as ADHD. It has been shown that deficiencies in zinc [54], iron [55], magnesium [56], and omega-3 fatty acids [57], as well as the presence of synthetic additives including preservatives and colorants [58], elevate the risk of ADHD in children (inattention, anxiety, impulsive behaviors, over-excitement, and carelessness). In this sense, diet interventions have been proposed as a potential therapy to decrease ADHD symptoms [59]. In addition, it has been noted that an optimal maternal diet during pregnancy may be even more important in protecting against childhood ADHD than the diet itself during early childhood [60]. In fact, it has been suggested that supplements of omega-3 fatty acids and some deficit minerals could reduce medication dosage and ADHD symptoms [61, 62]. There is an important relationship between omega-3 fatty acids and the gut microbiome with ADHD. Omega-3 fatty acids elevate neuroprotective factors, such as BDNF and GDNF, and reduce pro-inflammatory cytokines in the brain [63, 64]. Omega-3 fatty acids and the gut microbiome show a bidirectional relationship. *In vivo* study on mice has shown that dietary supplementation with *Bifidobacterium breve* elevated the arachidonic acid (AA) and DHA in the brain of animals. In addition, omega-3 supplementation in pregnant mice caused a significant elevation of *Lactobacillus* and *Bifidobacterium* in their offsprings during adulthood [65].

3. PI3K; UPSTREAM AND DOWNSTREAM SIGNALING PATHWAYS

Phosphoinositide 3-kinases (PI3Ks) are complex enzymes belonging to a highly conserved family of lipid kinases that play a key role in various metabolic processes. PI3Ks transduce metabolic and mitogenic signals modulating multiple aspects of cell physiology, such as proliferation, migration, apoptosis, and cell growth [66]. According to their structure and substrate specificity, PI3Ks consist of eight isoforms classified into three categories of I, II, and III that operate in a sequence of events [67, 68]. In the first signal transduction step, class III PI3Ks phosphorylate phosphatidylinositol (PtdIns) followed by further phosphorylation by class II and I PI3Ks [69].

The main substrates of class II and III PI3Ks are PtdIns-3, 4P, and PtdIns-4P, whereas class I PI3Ks is responsible for the production of PtdIns-3P by converting PtdIns into 3-phosphoinositides [70, 71]. Class I PI3Ks are functional heterodimers of regulatory and catalytic subunits with molecular weights of 85 kDa (p85) and 110 kDa (p110), respectively, having different isoforms [72]. Class II and III PI3Ks have different structures and functions from class I. Class II lacks Asp residue on the C-terminal C2 domain, which is needed to bind Ca^{2+}; thus, it is suggested that class II binds lipids in a Ca^{2+}-independent manner [73]. Class II has three catalytic subunits with no regulatory protein [67]. Class III is a heterodimer consisting of a catalytic and a regulatory protein with limited known roles, such as the trafficking of proteins and vesicles [74]. PI3K signaling pathway is a redox-dependent regulation pathway that plays an important role in regulating vital biological processes, such as cell growth, survival, proliferation, and motility, as well as redox modification [75]. Homeostasis of cellular redox is the first line of defense against various stimuli and is very important for many biological processes [76].

Multiple upstream signaling pathways coupled to a broad range of membrane receptors, including ephrin / EphB, leptin, and ErbB (erythroblastic leukemia viral oncogene homolog) as receptor tyrosine kinases (RTKs), in addition to endothelin, neurokinin-1 (Nk1), and chemokines as G-protein coupled receptors (GPCRs), are involved in the activation of PI3K class I [77, 78]. The activation of PI3K *via* GPCRs principally occurs by two possible mechanisms of active Ras or Gβγ. On the contrary, β-arrestin acts as a negative regulator of GPCRs to mediate the inhibition of PI3K. In addition, Janus kinase (JAK) and insulin receptor substrate 1 (IRS1) mediate the activation of PI3K by RTKs [79]. According to evidence, there is also a tight linkage in which PI3K/protein kinase B (Akt) signaling pathway, as well as N-Methyl-D-aspartate (NMDA) [80], Toll-like, and morphine [81] receptors, regulate each other [82].

In general, the catalytic domain of PI3K binds to Ras or Rac subfamily of GTP hydrolases, while an SH_2 domain of the regulatory subunits binds to IRS1 as adaptor proteins or phosphotyrosyl residues on tyrosine kinase receptors to mediate the binding to GPCRs [83], activating Ras/Raf/MEK/ERK [84, 85] and mitogen-activated protein kinases (MAPK) pathways [86]. To meet this requirement, the PI3K/Akt signaling pathway should orchestrate a complex set of upstream and downstream pathways. These processes induce the translocation of glucose transporter (GLUT) to the membrane, thus increasing glucose uptake and multiplying the downstream cascades [69, 87]. Improper PI3K / Akt signaling contributes to increased reactive oxygen species (ROS) levels *via* direct mitochondrial bioenergetics modulation and activation of NADPH oxidases (NOX) or indirectly via the production of ROS as a metabolic byproduct [88].

Phosphorylated lipids are produced in cell membranes during signaling events and contribute to the activation and recruitment of several downstream signaling components, which are promptly metabolized by lipid phosphatases, such as PTEN (phosphatase and tensin homolog deleted on chromosome ten), to terminate PI3K signaling [89]. PI3Ks also activate downstream signaling pathways in a sequence of events by catalyzing the phosphorylation of phosphatidylinositol at the 3-hydroxyl position of the inositol ring [20, 69, 90]. Compared to other effectors, PI3K seems to play the most important role in the universal activation of Akt, which displays a tight coupling with PI3K. Indeed, the phosphorylation of Akt functions as a replacement for PI3K activation [91]. PI3K phosphorylates Akt and stimulates its catalytic activity, which, in turn, results in the phosphorylation of other signaling mediators modulating cell growth and survival. In fact, the phosphorylation of Akt is sufficient and necessary to mediate other downstream signaling pathways [91]. Likewise, it has been reported that Akt phosphorylation of Bad as an apoptosis-inducing protein prevents the binding of Bad to Bcl-2 and thus, improves cell survival [92]. The phosphorylation of Akt also subsets the activity of some me-

diators, such as forkhead box subgroup O (FoxO) transcription factors [93], as well as hypoxia-inducible factor 1 (HIF-α) [94] and tuberous sclerosis (TSC) [66]. Following that, Akt phosphorylates a constitutively active protein named glycogen synthase kinase 3 (GSK3), which, in turn, phosphorylates glycogen synthase, c-M yc [95], and cyclin D as down-stream mediators inactivating them. The inactivation process causes the subsequent activation of pathways which are normally suppressed by these mediators [66, 78].

PI3K/Akt and Ras/ERK also lead to the activation of mammalian target of rapamycin (mTOR) [96-98] which, in turn, phosphorylates downstream effectors to represent anabolic metabolism and support cell proliferation and growth [99]. As two direct substrates of mTOR, S6 kinase-1 (S6K1) activates glycolysis and the biosynthesis of lipid, nucleotide, and protein [100] and the eukaryotic initiation factor-4E (eIF4E)-binding proteins (4EBPs) regulate cell proliferation and survival [101].

In addition, PI3K activity initiates Akt-independent signaling cascades that affect cellular metabolisms like cAMP response element-binding protein (CREB) and serum- and glucocorticoid-induced kinase (SGK) family [66]. Notably, there is much evidence suggesting that SGK and CREB play a key role in Akt-independent signaling [66, 102]. Keeping the complex PI3K/Akt/ mammalian target of rapamycin (mTOR) network homeostatically balanced is important to avoid aberrant cellular proliferation and maintain glucose homeostasis. Recent research has revealed the key downstream role of PI3K catalytic subunits in the effects of insulin or leptin on hypothalamic neurons differentiation [103].

Altogether, the evidence revealed a double edge role that PI3K plays in the production of inflammatory cytokines [104]. On the one hand, the activation of Toll-like receptors (TLRs) recruit PI3Ks and downregulate the production of nuclear factor-κB (NF-κB)-induced pro-inflammatory cytokines [104]. In line with this, the loss of functional PI3K decreases TLR4 internalization, increasing pro-inflammatory and decreasing anti-inflammatory cytokines [105]. On the other hand, an important role of PI3K in the downstream of chemokine G protein-coupled receptor (GPCR) has been revealed during inflammation [79]. Activation of TLR4 mediates PI3K signaling, induces inflammation, and causes neuroinflammation [106, 107]. Besides, transforming growth factor-beta (TGF-1β) exerts anti-inflammatory effects through PI3K, as well as its downstream signaling pathways [108]. Fig. (**1**) displays the upstream and downstream signaling pathways of PI3K.

4. THE FUNCTION OF PI3K SIGNALING PATHWAY IN BRAIN DEVELOPMENT AND NEUROGENESIS

Neurogenesis has been selected as one of the topics of interest since the brain has been shown to be able to produce new nerve cells [109]. Neurogenesis has a significant role in the dentate gyrus, producing excitatory granule neurons related to memory and learning [110]. The PI3K signaling pathway has been shown to be one of the pathways affecting endogenous neurogenesis [111]. The key role of PI3K in neurons has also been confirmed by its association in acute brain pathologies, for example, developmentally-related brain abnormalities [112, 113], epilepsy [114, 115], aging-related neurodegeneration [116, 117], and brain cancer [118, 119]. Diverse research has indicated that dysregulated signaling of PI3K/Akt in neurons has a number of damaging consequences, including increased ROS levels, membrane depolarization, mitochondrial fragmentation, and declined oxidative phosphorylation and ATP production [120-123]. Activation of the PI3K pathway has been reported to contribute to the preservation of neurons and the brain against ischemic injury. For instance, vascular endothelial growth factor (VEGF) preserves the brain after focal cerebral ischemia *via* activation of the PI3K pathway [124].Various combinations of PI3K isoforms may lead to several functional events depending on the metabolic context, upstream signals, and interconnection of various cellular pathways. In this sense, in sensory neurons, p110δ is a vital signaling component for efficient axonal elongation in the developing and regenerating nervous system [125]. Hereon, the inactivation of the p110δ produces defective axonal elongation and prevents axonal regeneration in a model of sciatic nerve crush injury [125]. Amyloid peptide complexes present in Alzheimer's disease (AD) induce continuous stimulation of Akt, which, in turn, phosphorylates the mitochondrial fission protein GTPase dynamin-related protein 1 (Drp1). This mechanism is suggested to be involved in the fragmented mitochondrial components observed in this disease. Previous research works have shown that the stimulation of the PI3K pathway increases neuronal cell life in stressful situations [126-128]. These findings were followed by other studies that focused on complementing or identifying PI3K activators to prevent neuronal death. According to a study by Rui Zheng *et al.* carried out in a mouse model of AD, selenomethionine promoted neurogenesis in the hippocampus *via* the PI3K-Akt-GSK3β-Wnt pathway [129]. In another rat model of brain injury caused by surgical injury (SBI), PI3Kγ stimulated the pro-inflammatory phenotype. It has also been reported that the pharmacological inhibitors of PI3Kγ (AS252424 or AS605240) enhanced neurological function after SBI [130].

5. ROLE OF PI3K IN ADHD

As mentioned before, PI3K is involved in synaptic plasticity and neurogenesis. One of the important mechanisms for regulating AMPH-induced dopamine efflux through DAT modulation is the CADM1 (Cell adhesion molecule 1)/PI3K/Akt pathway [32]. CADM1 belongs to a group of scaffolding proteins associated with membrane guanylate kinase homologs [131]. PI3K is recruited to the cytoplasmic domain of CADM1 and leads to actin reorganization and cell spread through activation of Akt [132]. Consequently, the downregulation of the PI3K/Akt pathway reduces cell spread. Thus, the PI3K/AKT pathway is essential for CADM1 mediated signals and may be a novel mechanism for DAT modulation and dopamine efflux by AMPH [32]. Several studies have shown that PI3K has major effects on DAT cellular distribution [133, 134]. For example, insulin regulates DAT expression *via* activating PI3K/Akt pathway [135]. Another study using LY294002, an inhibitor of PI3K, demonstrated that the inhibition of PI3K results in the internalization of DAT and a decrease in transport capacity [136]. The use of inhibitors has been considered as a factor to evaluate the importance of PI 3-kinases in various functional

settings [137]. *In vitro* studies have demonstrated that LY294002 prevents the effects of phentermine and methamphetamine on the expression of DAT, suggesting that the beneficial effects of these AMPH are related to modulation of the PI3K/Akt pathway [138, 139]. Brandon and colleagues indicated that LY294002 reduces AMPH-induced dopamine efflux through alterations in DAT cell surface expression quantified by transient current analysis [134]. Collectively, PI3K signaling carries DAT on the cell surface, which is essential for stimulating dopamine efflux by AMPH and thus increasing extracellular dopamine levels.

Norepinephrine (NE) is another important neurotransmitter involved in ADHD since it affects cognitive functions in the prefrontal cortex [140, 141]. Excessive activity of the cAMP–CREB pathway in the locus coeruleus (LC) leads to an elevated NE transmission in the frontal cortex and disturbs cognitive functions [142]. A study on PI3Kγ knockout mice revealed that PI3K balances the cAMP–CREB pathway through the activation of PDE4D and improves the function of LC. PI3Kγ knockout mice showed overactivity of the cAMP-CREB pathway in LC, high concentrations of NE, and ADHD symptoms (Fig. **1**) [22].

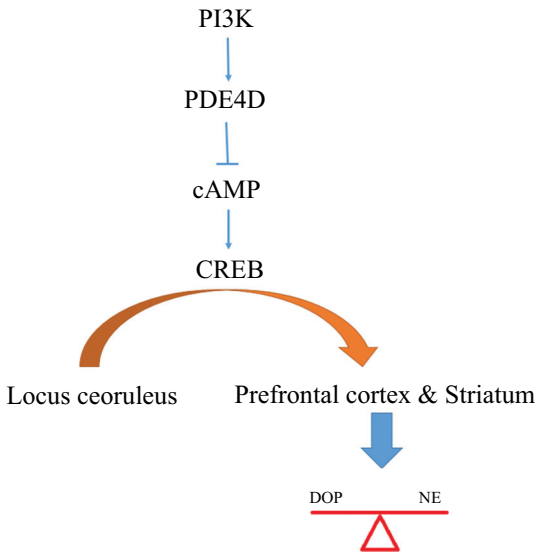

Fig. (1). Relationships between PI3K and ADHD. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

It has been indicated that the adenosine ADORA2A gene is involved in the etiology of ADHD [143]. Catiane *et al.* showed that caffeine, a non-selective antagonist of adenosine A1 (A1R) and A2A (A2AR) receptors, and SCH 58261, an $A_{2A}R$ antagonist, have beneficial effects in improving axonal outgrowth of neurons isolated from the ADHD rat model *via* activation of PI3K signaling [23]. The beneficial effects were reversed by the co-administration of PI3K inhibitor LY 294002.

One important protein in the regulation, maturation, and proliferation of neurons, which is modulated by PI3K, is mTOR. According to previous studies, there is a link between ADHD and low levels of docosahexaenoic (DHA) and eicosapentaenoic (EPA) fatty acids. The neuroprotective effects of DHA and EPA are related to the activation of PI3K/Akt/mTOR pathways, alleviating the symptoms of ADHD [37].

6. NATURAL AND SYNTHETIC PI3K SIGNALING PATHWAY MODULATORS

Neuroprotective agents are the basis for targeting the manifestation and phosphorylation of the PI3K/Akt pathway [144]. Many natural products, including caffeine, epigallocatechin-3-gallate (EGCG), celastrol, butein, capsaicin, β-elemene, *etc.*, have been reported to target PI3K/Akt/mTOR pathway [145]. Oxymatrine (OMT) is a quinolizidine alkaloid isolated from the old-style Chinese herbal medicine *Sophora japonica* [146]. It has been established that OMT has low toxicity with pharmacological actions, including anti-inflammation [147], antioxidant [148], and neuroprotection activities [149]. The main outcomes of research conducted by Yue Liu *et al.* proved that OMT is able to protect the brain from damage in *in vivo* and the hippocampal neurons in *in vitro*. The protective effects could be attributed to the modulation of proteins associated with apoptosis leading to the downregulation of NR2B and PI3K/Akt/GSK3β pathway [150]. Notoginsenoside R1 (NGR1) is the main phytoestrogen compound isolated from *Panax notoginseng*. NGR1 has remarkable antioxidant, anti-apoptotic and anti-inflammatory effects that may play an important role against cardiac dysfunction, severe liver failure, and diabetic kidney infection [151]. Another study showed that NGR1 inhibits neuronal apoptosis and promotes neuronal survival, exerting important neuroprotective effects against hypoxic-ischemic brain damage (HIBD) in neonates by targeting ERs and regulating the PI3K/Akt/mTOR/JNK signaling pathway [152]. EGCG, the most abundant catechin in green tea, has shown several useful effects, including anti-cancer activity. EGCG has also been reported to inhibit the migration and/or metastasis of melanoma cells, by inhibiting the PI3K and other signaling pathways such as extracellular signal-regulated protein kinase (ERK) and focal adhesion kinase (FAK) [153]. The modulatory effects of EGCG on protein kinase C and PI3K are associated with neuroprotection and a decrease in nigral impairment by chelating free radicals and reducing oxidative stress [154].

Taxifolin or dihydroquercetin is a natural compound and health supplement product that could be found in the silymarin extract from the milk thistle (*Silybum marianum*) seeds. Taxifolin prevents the development, relocation, and invasion of human osteosarcoma cells by decreasing the expression levels of AKT [155, 156]. Taxifolin overpowers UV-reduced skin carcinogenesis by targeting EGFR and PI3K [157]. Vitexin (apigenin-8-C-glucoside), a dynamic component of many old-style Chinese drugs, is naturally present in numerous medical herbals, such as *Vitex agnus-castus* or *Phyllostachys nigra*. The compound has various pharmacological properties like antioxidant, neuroprotective, and anti-inflammatory effects [158]. In one study, vitexin was assessed for its *in vivo* anticancer action in nude xenografted mice with human lung carcinoma A549 cells. Vitexin induced cytochrome c release from the mitochondria to cytosol, and the mitochondrial membrane potential loss led to apoptosis. The treatment with vitexin significantly reduced the levels of p-PI3K, p-Akt, and p-mTOR, whereas this pro-

apoptotic effect on A549 cells was also partially blocked by the presence of the Akt activator SC79 [159].

A study by James Ahn *et al.* showed that other natural compounds, including *Bacopa monnieri*, *Ginkgo biloba*, Ginseng, and Valerian (*Valeriana officinalis*), are effective in treating ADHD through various mechanisms, such as neuroprotection, regulation of dopamine, improvement in cerebrovascular blood flow, nootropic effect on the central nervous system (CNS,) and inhibition of the breakdown of GABA in the CNS [160]. In addition, many studies indicated that these natural products affect PI3K signaling pathway. *Bacopa monnieri* L. Wettst is a dietary supplement that has been found to play an important role in cognitive health and function [161]. It has been reported that this plant can play a protective role in SH-SY5Y cells against tert-butyl hydroperoxide-induced cell death by activating the ERK/MAPK and PI3K/Akt signaling pathways [162]. Bacopaside I, a triterpenoid found in *Bacopa monnieri,* extract can be effective in neuroprotection of animal models *via* PKC and PI3K/Akt pathways [163]. *Ginkgo biloba* L (GB) is a Chinese medicinal plant belonging to the Ginkgoaceae family, which has many uses in medicine [164]. *Ginkgo biloba* extract (GBE) has neurological properties since it modulates the growth of neurites and can activate the PI3K/Akt/mTOR pathway [165]. GBE exerts its protective role in different ways. For example, in an indirect way, it activates the PI3K/Akt /mTOR pathway through inhibition of GSK3, which is related to neurogenesis, proliferation, and migration [166, 167]. Ginseng is another natural product that has been used as a traditional herbal medicine for over 2000 years and is recorded to have antianxiety, antidepressant, and cognition-enhancing properties [168]. Ginseng inhibits brain ischemia/perfusion damage in mice by inhibiting apoptosis *via* activating the PI3K/Akt/mTOR signaling pathway [168]. Red ginseng butter extract (KRG) has been shown to be effective in inhibiting oxidative stress-induced apoptosis in neuroblastoma cells. This inhibition is mediated by the restoration of the ER-β through the upregulation of the PI3K/Akt signaling pathway [169]. Valerian, as a natural product with medicinal and antispasmodic properties, affects the nervous system. The role of this plant in the treatment of hyperactivity has been evaluated [170]. In one study, 30 children aged 5 to 11 years with hyperactivity used valerian tincture every day for two weeks. This treatment had a significant effect in reducing the symptoms of ADHD, especially attention span and persistent impulsivity and/or hyperactivity [171, 172].

In an *in vivo* assay, it was reported that traumatic brain injury (TBI) causes apoptosis. It has been shown that FTY720, as a synthetic immunosuppressive agent, improved neurobehavioral function after TBI and reduced apoptosis by modulating diverse apoptotic indicators, like Bcl-2, Bcl-xL, Bax, and cytochrome c. Moreover, FTY720 induced the PI3K/AKT and autophagy pathways, responsible for the neuroprotective effects, since PI3K and autophagy inhibitors reversed these protective effects induced by FTY720 [173].

Amphetamine is another synthetic modulator that increases PI3K and pSTAT3. A study aimed at suppressing appetite with amphetamine showed that amphetamine suppresses appetite by inhibiting neuroprotein Y (NPY) neurons, activating pro-opiomelanocortin (POMC) neurons in the hypothalamus, and increasing PI3K, STAT3, and MC3 receptors [174]. Clonidine extended release treatment is effective in children and adolescents with ADHD or Tourette's disorder [175]. Analysis of vascular response in normal mice showed that the clonidine-induced relaxation was reduced by inhibiting the PI3K/Akt/eNOS pathway [176]. Modafinil is an effective drug for the treatment of ADHD [177]. The results of a study focused on treating ADHD showed that modafinil in sleep-deprived mice inhibited autophagy and apoptosis and increased PI3K/Akt/mTOR/P70S6K signaling pathway activity in hippocampal neurons, leading to improved learning and memory [178]. The main negative regulator of the PI3K/Akt signaling pathway is phosphatase and tensin homolog deleted on chromosome ten (PTEN). Therefore, modulating PTEN expression or promoting its activation can play an important role in modulating cell function [179]. The outcomes of a study showed that the inhibition of PTEN leads to neuronal survival, light protection, and neuronal regeneration. These factors also play an important role in activating Akt, which leads to axonal myelination. In fact, by inhibiting PTEN, tissue damage and nerve cell death can be prevented, and neuronal function can improve [180]. P2X7, as an upstream modulator of the PI3K/Akt pathway, has a significant effect on neuroblastoma extracellular cells and regulates neuronal differentiation [181-183]. P2X7 also plays an important role in the expression of HIF1α, PI3K/Akt activation, VEGF secretion, GSK3β inactivation, and regulation of MYCN oncogene and glycogen secretion [184].

7. ADVANTAGES AND DISADVANTAGES OF PI3K SIGNALING PATHWAY MODULATORS

As a core protein, PI3K orchestrates a variety of signaling pathways, through which it mediates an extraordinarily broad range of cellular functions, such as cell proliferation, growth, survival, migration, metabolism, secretion, and signal transduction in all tissue types [16]. However, PI3K could play a dual role as a double-edged knife. Dysfunctions in the PI3K pathway correlate with some disorders, like type II diabetes [66] and ADHD [18], while the hyperactivation of the pathway is correlated with cancer [22] and some neurodegenerative diseases [185, 186]. Besides, alterations in PI3K signaling also lead to immunological, cardiovascular, and neurological diseases. In this sense, the double function of PI3K has been reported to depend on the upstream signaling pathways, the metabolic context, and crosstalk between cellular pathways.

Significant evidence suggests that due to the increased activation of upstream signaling pathways, PI3K mutation, or loss of PTEN activity, elevated levels of PI3K and PtdIns-3,4,5-P3 contribute to tumorigenesis [187]. In a meta-analysis, PI3K and PTEN were found to be the second and third most mutated genes in cancers [89]. The NMDA receptor of the spinal cord mediated the activation of PI3K downstream mTOR in the pathogenesis of cancer pain [80]. Over the last decades, PI3Ks inhibitors have been tested in clinical trials as a therapy against cancer [188]. However, these non-selective PI3K inhibitors have significant side effects, thus limiting their potential use in cancer treatment. Limiting the dose and improving the specificity of antagonist function can lead to better efficacy and fewer toxicity profiles [69, 77, 188].

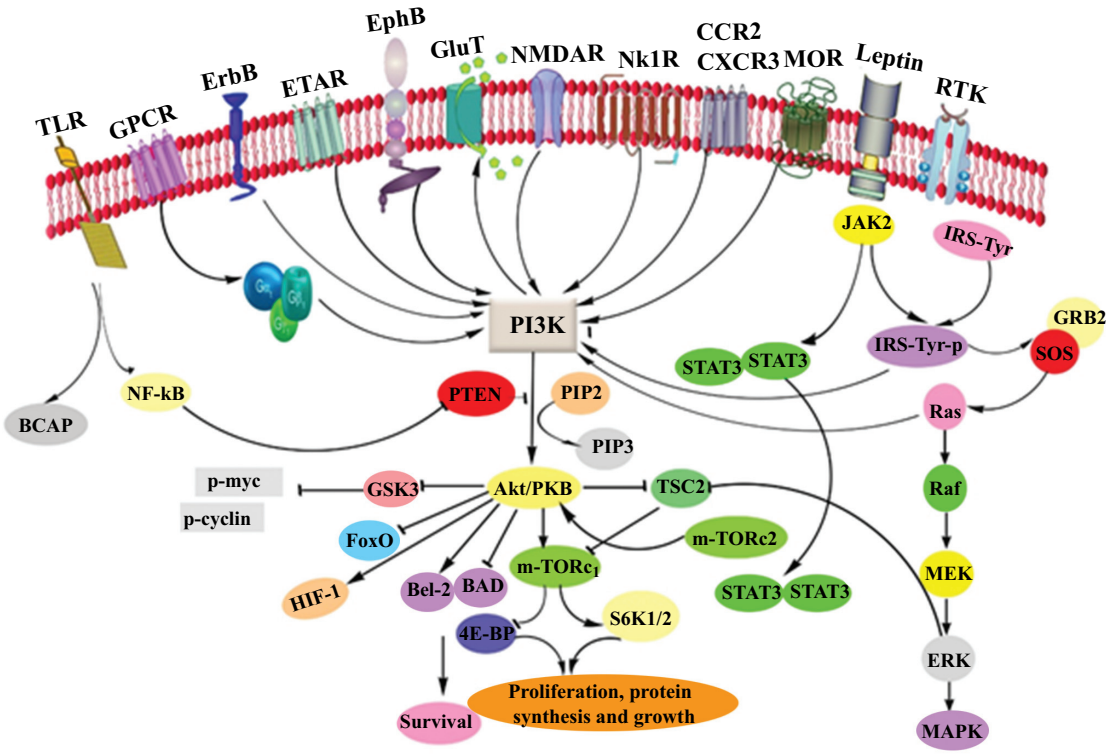

Fig. (2). The upstream and downstream signaling pathways of PI3K, and related changes in diseases. TLR: Toll-like receptor, GPCR: G protein-coupled receptor, ETAR: Endothelin A receptor, EphB: Ephrin-B, GluT: Glucose transporter, NMDAR: N-methyl-D-aspartate receptor, Nk1R: neurokinin 1 receptor, CCR2 and CXCR3: Chemokine receptors, MOR: Morphine receptor, RTK: Receptor tyrosine kinase, NF-kB: Nuclear factor kappa-B, PI3K: Phosphoinositide 3-kinase, IRS: Insulin receptor substrate, GSK-3: Glycogen synthase kinase-3, HIF-1: Hypoxia-inducible factors, mTOR: Mammalian target of rapamycin, PIP2: Phosphatidylinositol 4,5-bisphosphate, PIP3: Phosphatidylinositol (3,4,5)-trisphosphate *.(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

PI3K activation through different upstream pathways in the central nervous system creates the core path of PI3K/Akt/mTOR in regulating synapse formation, neuronal development, neuronal integration, maturation, and proliferation in the brain [189]. The importance of the PI3K signaling pathway in neuronal function is due to its involvement in the pathology of various diseases, including epilepsy [114], neurodegeneration and aging [116, 117, 190], neuronal differentiation, neurogenesis, neuroprotection [191], brain malformations [113] memory performance, neuronal plasticity, signal transduction, and vesicle trafficking [16]. Since PI3K/Akt mediators are needed at an intermediate level for cell survival, the deletion of PTEN causes cell death [192] and hypermyelination [193], while the increased activation of PI3K/Akt/mTOR signaling is found in a number of brain disorders, especially diverse cases of hemimegaloencephaly [194]. As a downstream signaling pathway of nerve growth factor (NGF), PI3K/Akt/NF-κB induced neuronal differentiation through the expression of the opioid receptor [195] and ephrinB1-induced activation of PI3K/Akt signaling pathway associated with pain [196].

From a behavioral point of view, Akt knockout mice showed cognitive defects and microcephaly derived from mTOR blockage [197]. Neuronal dysregulation of the PI3K/Akt [123] pathway results in membrane depolarization, mitochondrial fragmentation, and increased oxidative stress [120]. Both overexpression and knockout of PI3K resulted in the reduction of spatial memory [121]. Consequently, in AD, β-amyloid induces an excessive level of Akt, which, in turn, causes mitochondrial dysfunction [120-122].

In a study by Darcq and Kieffer, the PI3K knockout mouse has also been suggested to be a promising ADHD model for developing novel therapeutic agents [18].

Altogether, an intermediate and not excessive level of PI3K/Akt is suggested to be the central node to integrate necessary developmental signals for brain development, repair, and plasticity, since most neurons in the cerebellum, cerebral cortex, and hippocampus express PI3K at high levels. As previously described, PI3K could play either a positive or negative role in the inflammatory conditions. Thus, its double function depends on the upstream signaling pathways, metabolic context, its level, and interconnection of cellular pathways. Finally, further research is needed to unveil the new roles of PI3K in different physiological and pathological situations. Fig. (**2**) also shows the changes in PI3K during diseases. Under inflammatory conditions, ZSTK474 (a PI3K inhibitor) showed anti-inflammatory effects in a mice model of cerebral ischemia/reperfusion [198]. In this line, Leng *et al.* reported that the activation of the PI3K/Akt signaling pathway and the inhibition of GSK3 mediate the neuroprotective effects of valproic acid as a mood-stabilizer [199].

In the context of ADHD disorder, D'andrea *et al.* reported the involvement of a kinase-independent but CREB-dependent mechanism through which PI3K regulates ADHD-related behaviors to control noradrenergic/dopamine in prefrontal cortex and striatum *via* NA neurons of locus coeruleus (LC). As PI3K has an essential role in the management of noradrenergic neurons, it opens new insights into ADHD [22].

CONCLUSION

ADHD is a complex neurological disorder that is associated with a variety of symptoms, such as poor academic performance, poor family relationships, anxiety, depression, and antisocial behaviors, and leads to a decline in quality of life. PI3Ks, are a family of highly evolutionarily conserved enzymes and modulators of cellular metabolism that play an essential role in the management of noradrenergic neurons and ADHD. The available data seem to support that natural and synthetic inhibitors of the PI3K signaling pathway could be a promising therapeutic approach for neurological diseases, including ADHD. However, the information available is very preliminary, and future studies at different levels are necessary to confirm these promising data.

AUTHORS' CONTRIBUTION

SS and MS contributed to the conception of the manuscript. SS, TN, SF, AS, and ES drafted the manuscript. Finally, all the authors critically revised the manuscript and gave the final approval.

LIST OF ABBREVIATIONS

ADHD	=	Attention-Deficit Hyperactivity Disorder
AMPH	=	Amphetamine
ADORA2A	=	Adenosine A2A Receptor
BDNF	=	Brain-derived Neurotrophic Factor
CD	=	Conduct Disorder
MD	=	Mitochondrial Dysfunction
OS	=	Oxidative Stress
CREB	=	cAMP Response element-binding Protein
DAT	=	Dopamine Transporter
EGCG	=	Epigallocatechin-3- gallate
FoxO	=	Forkhead Box Subgroup O
GSK3	=	Glycogen Synthase Kinase 3
GLUT	=	Glucose Transporter
HIF-α	=	Hypoxia-inducible Factor 1
LBW	=	Low Birth Weight
mTOR	=	Mammalian Target of Rapamycin
NE	=	Norepinephrine
Nk1	=	Neurokinin-1
NGR1	=	Notoginsenoside R1
NF-κB	=	Nuclear Factor-κB
NMDA	=	N-Methyl-D-aspartate
ODD	=	Oppositional Defiant Disorder
OMT	=	Oxymatrine
PI3K	=	Phosphoinositide 3-kinase
PtdIns	=	Phosphatidylinositol
ROS	=	Reactive Oxygen Species
TLRs	=	Toll-like Receptors
VEGF	=	Vascular Endothelial Growth Factor
CNS	=	Central Nervous System
PTEN	=	PHOSPHATASE and Tensin Homolog Deleted on Chromosome Ten
TBI	=	Brain Injury

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

A. Sureda was supported by Instituto de Salud Carlos III through the Health Research Fund (Project CIBEROBN CB12/03/30038).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Evans, S.; Ling, M.; Hill, B.; Rinehart, N.; Austin, D.; Sciberras, E. Systematic review of meditation-based interventions for children with ADHD. *Eur. Child Adolesc. Psychiatry,* **2018**, *27*(1), 9-27. http://dx.doi.org/10.1007/s00787-017-1008-9 PMID: 28547119

[2] Luo, Y.; Weibman, D.; Halperin, J.M.; Li, X. A review of heterogeneity in attention deficit/hyperactivity disorder (ADHD). *Front. Hum. Neurosci.,* **2019**, *13*, 42. http://dx.doi.org/10.3389/fnhum.2019.00042 PMID: 30804772

[3] Skogli, E.W.; Teicher, M.H.; Andersen, P.N.; Hovik, K.T.; Øie, M. ADHD in girls and boys--gender differences in co-existing symptoms and executive function measures. *BMC Psychiatry,* **2013**, *13*(1), 298. http://dx.doi.org/10.1186/1471-244X-13-298 PMID: 24206839

[4] Núñez-Jaramillo, L.; Herrera-Solís, A.; Herrera-Morales, W.V. ADHD: Reviewing the causes and evaluating solutions. *J. Pers. Med.,* **2021**, *11*(3), 166. http://dx.doi.org/10.3390/jpm11030166 PMID: 33804365

[5] Reale, L.; Bartoli, B.; Cartabia, M.; Zanetti, M.; Costantino, M.A.; Canevini, M.P.; Termine, C.; Bonati, M. Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *Eur. Child Adolesc. Psychiatry,* **2017**, *26*(12), 1443-1457. http://dx.doi.org/10.1007/s00787-017-1005-z PMID: 28527021

[6] Castellanos, F.X.; Sonuga-Barke, E.J.; Milham, M.P.; Tannock, R. Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends Cogn. Sci.,* **2006**, *10*(3), 117-123. http://dx.doi.org/10.1016/j.tics.2006.01.011 PMID: 16460990

[7] Costa Dias, T.G.; Iyer, S.P.; Carpenter, S.D.; Cary, R.P.; Wilson, V.B.; Mitchell, S.H.; Nigg, J.T.; Fair, D.A. Characterizing heterogeneity in children with and without ADHD based on reward system connectivity. *Dev. Cogn. Neurosci.,* **2015**, *11*, 155-174.

http://dx.doi.org/10.1016/j.dcn.2014.12.005 PMID: 25660033

[8] Faraone, S.V. Attention deficit hyperactivity disorder and premature death. *Lancet,* **2015**, *385*(9983), 2132-2133. http://dx.doi.org/10.1016/S0140-6736(14)61822-5 PMID: 25726517

[9] Öğütlü, H.; Esin, İ.S.; Erdem, H.B.; Tatar, A.; Dursun, O.B. Mitochondrial DNA copy number is associated with attention deficit hyperactivity disorder. *Psychiatr. Danub.,* **2020**, *32*(2), 168-175. http://dx.doi.org/10.24869/psyd.2020.168 PMID: 32796781

[10] Russell, V.A. Hypodopaminergic and hypernoradrenergic activity in prefrontal cortex slices of an animal model for attention-deficit hyperactivity disorder--the spontaneously hypertensive rat. *Behav. Brain Res.,* **2002**, *130*(1-2), 191-196. http://dx.doi.org/10.1016/S0166-4328(01)00425-9 PMID: 11864734

[11] Sagvolden, T.; Johansen, E.B.; Aase, H.; Russell, V.A. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav. Brain Sci.,* **2005**, *28*(3), 397-419. http://dx.doi.org/10.1017/S0140525X05000075 PMID: 16209748

[12] Feldman, H.M.; Reiff, M.I. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. *N. Engl. J. Med.,* **2014**, *370*(9), 838-846. http://dx.doi.org/10.1056/NEJMcp1307215 PMID: 24571756

[13] American Psychiatric Association. *A.; Association, A. P., Diagnostic and statistical manual of mental disorders: DSM-5*; American psychiatric association: Washington, DC, **2013**.

[14] Taylor, L.E.; Antshel, K.M. Factors associated with parental treatment attitudes and information-seeking behaviors for childhood ADHD. *J. Atten. Disord.,* **2021**, *25*(4), 607-617. http://dx.doi.org/10.1177/1087054718821734 PMID: 30623746

[15] Nimmo-Smith, V.; Merwood, A.; Hank, D.; Brandling, J.; Greenwood, R.; Skinner, L.; Law, S.; Patel, V.; Rai, D. Non-pharmacological interventions for adult ADHD: A systematic review. *Psychol. Med.,* **2020**, *50*(4), 529-541. http://dx.doi.org/10.1017/S0033291720000069 PMID: 32036811

[16] Sánchez-Alegría, K.; Flores-León, M.; Avila-Muñoz, E.; Rodríguez-Corona, N.; Arias, C. PI3K signaling in neurons: A central node for the control of multiple functions. *Int. J. Mol. Sci.,* **2018**, *19*(12), 3725. http://dx.doi.org/10.3390/ijms19123725 PMID: 30477115

[17] Williams, J.M.; Owens, W.A.; Turner, G.H.; Saunders, C.; Dipace, C.; Blakely, R.D.; France, C.P.; Gore, J.C.; Daws, L.C.; Avison, M.J.; Galli, A. Hypoinsulinemia regulates amphetamine-induced reverse transport of dopamine. *PLoS Biol.,* **2007**, *5*(10), e274. http://dx.doi.org/10.1371/journal.pbio.0050274 PMID: 17941718

[18] Darcq, E.; Kieffer, B.L. PI3K signaling in the locus coeruleus: A new molecular pathway for ADHD research. *EMBO Mol. Med.,* **2015**, *7*(7), 859-861. http://dx.doi.org/10.15252/emmm.201505266 PMID: 25925427

[19] Aston-Jones, G.; Rajkowski, J.; Cohen, J. Role of locus coeruleus in attention and behavioral flexibility. *Biol. Psychiatry,* **1999**, *46*(9), 1309-1320. http://dx.doi.org/10.1016/S0006-3223(99)00140-7 PMID: 10560036

[20] Cantley, L.C. The phosphoinositide 3-kinase pathway. *Science,* **2002**, *296*(5573), 1655-1657. http://dx.doi.org/10.1126/science.296.5573.1655 PMID: 12040186

[21] Kim, J-I.; Lee, H-R.; Sim, S.E.; Baek, J.; Yu, N-K.; Choi, J-H.; Ko, H-G.; Lee, Y-S.; Park, S-W.; Kwak, C.; Ahn, S.J.; Choi, S.Y.; Kim, H.; Kim, K.H.; Backx, P.H.; Bradley, C.A.; Kim, E.; Jang, D.J.; Lee, K.; Kim, S.J.; Zhuo, M.; Collingridge, G.L.; Kaang, B.K. PI3Kγ is required for NMDA receptor-dependent long-term depression and behavioral flexibility. *Nat. Neurosci.,* **2011**, *14*(11), 1447-1454. http://dx.doi.org/10.1038/nn.2937 PMID: 22019731

[22] D'Andrea, I.; Fardella, V.; Fardella, S.; Pallante, F.; Ghigo, A.; Iacobucci, R.; Maffei, A.; Hirsch, E.; Lembo, G.; Carnevale, D. Lack of kinase-independent activity of PI3Kγ in locus coeruleus induces ADHD symptoms through increased CREB signaling. *EMBO Mol. Med.,* **2015**, *7*(7), 904-917. http://dx.doi.org/10.15252/emmm.201404697 PMID: 25882071

[23] Alves, C.B.; Almeida, A.S.; Marques, D.M.; Faé, A.H.L.; Machado, A.C.L.; Oliveira, D.L.; Portela, L.V.C.; Porciúncula, L.O. Caffeine and adenosine A_{2A} receptors rescue neuronal development *in vitro* of frontal cortical neurons in a rat model of attention deficit and hyperactivity disorder. *Neuropharmacology,* **2020**, *166*, 107782. http://dx.doi.org/10.1016/j.neuropharm.2019.107782 PMID: 31756336

[24] Tarver, J.; Daley, D.; Sayal, K. Attention-deficit hyperactivity disorder (ADHD): An updated review of the essential facts. *Child Care Health Dev.,* **2014**, *40*(6), 762-774. http://dx.doi.org/10.1111/cch.12139 PMID: 24725022

[25] Faraone, S.V.; Perlis, R.H.; Doyle, A.E.; Smoller, J.W.; Goralnick, J.J.; Holmgren, M.A.; Sklar, P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol. Psychiatry,* **2005**, *57*(11), 1313-1323. http://dx.doi.org/10.1016/j.biopsych.2004.11.024 PMID: 15950004

[26] Faraone, S.V.; Mick, E. Molecular genetics of attention deficit hyperactivity disorder. *Psychiatr. Clin. North Am.,* **2010**, *33*(1), 159-180. http://dx.doi.org/10.1016/j.psc.2009.12.004 PMID: 20159345

[27] Fernández-Jaén, A.; Fernández-Mayoralas, D.M.; Calleja-Pérez, B.; Muñoz-Jareño, N.; López-Arribas, S. Genomic endophenotypes of attention deficit hyperactivity disorder. *Rev. Neurol.,* **2012**, *54*(Suppl. 1), S81-S87. PMID: 22374776

[28] Gizer, I.R.; Ficks, C.; Waldman, I.D. Candidate gene studies of ADHD: A meta-analytic review. *Hum. Genet.,* **2009**, *126*(1), 51-90. http://dx.doi.org/10.1007/s00439-009-0694-x PMID: 19506906

[29] Purper-Ouakil, D.; Wohl, M.; Mouren, M.C.; Verpillat, P.; Adès, J.; Gorwood, P. Meta-analysis of family-based association studies between the dopamine transporter gene and attention deficit hyperactivity disorder. *Psychiatr. Genet.,* **2005**, *15*(1), 53-59. http://dx.doi.org/10.1097/00041444-200503000-00009 PMID: 15722958

[30] Manor, I.; Eisenberg, J.; Tyano, S.; Sever, Y.; Cohen, H.; Ebstein, R.P.; Kotler, M. Family-based association study of the serotonin transporter promoter region polymorphism (5-HTTLPR) in attention deficit hyperactivity disorder. *Am. J. Med. Genet.,* **2001**, *105*(1), 91-95. http://dx.doi.org/10.1002/1096-8628(20010108)105:1<91::AID-AJMG1069>3.0.CO;2-V PMID: 11425009

[31] Grant, P.; Kuepper, Y.; Wielpuetz, C.; Hennig, J. Differential associations of dopamine-related polymorphisms with discrete components of reaction time variability: Relevance for attention deficit/hyperactivity disorder. *Neuropsychobiology,* **2014**, *69*(4), 220-226. http://dx.doi.org/10.1159/000360367 PMID: 24942140

[32] Kitagishi, Y.; Minami, A.; Nakanishi, A.; Ogura, Y.; Matsuda, S. Neuron membrane trafficking and protein kinases involved in autism and ADHD. *Int. J. Mol. Sci.,* **2015**, *16*(2), 3095-3115. http://dx.doi.org/10.3390/ijms16023095 PMID: 25647412

[33] Checa-Ros, A.; Jeréz-Calero, A.; Molina-Carballo, A.; Campoy, C.; Muñoz-Hoyos, A. Current evidence on the role of the gut microbiome in ADHD pathophysiology and therapeutic implications. *Nutrients,* **2021**, *13*(1), 249. http://dx.doi.org/10.3390/nu13010249 PMID: 33467150

[34] Bercik, P.; Denou, E.; Collins, J.; Jackson, W.; Lu, J.; Jury, J.; Deng, Y.; Blennerhassett, P.; Macri, J.; McCoy, K.D. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology,* **2011**, *141*(2), 599-609.e1-3. http://dx.doi.org/10.1053/j.gastro.2011.04.052 PMID: 21683077

[35] Dam, S.A.; Mostert, J.C.; Szopinska-Tokov, J.W.; Bloemendaal, M.; Amato, M.; Arias-Vasquez, A. The role of the gut-brain axis in attention-deficit/hyperactivity disorder. *Gastroenterology Clinics,* **2019**, *48*(3), 407-431. http://dx.doi.org/10.1016/j.gtc.2019.05.001 PMID: 31383279

[36] Kim, P.; Choi, C.S.; Park, J.H.; Joo, S.H.; Kim, S.Y.; Ko, H.M.; Kim, K.C.; Jeon, S.J.; Park, S.H.; Han, S.H.; Ryu, J.H.; Cheong, J.H.; Han, J.Y.; Ko, K.N.; Shin, C.Y. Chronic exposure to ethanol of male mice before mating produces attention deficit hyperactivity disorder-like phenotype along with epigenetic dysregulation of dopamine transporter expression in mouse offspring. *J. Neurosci. Res.,* **2014**, *92*(5), 658-670. http://dx.doi.org/10.1002/jnr.23275 PMID: 24510599

[37] Yde Ohki, C.M.; Grossmann, L.; Alber, E.; Dwivedi, T.; Berger, G.; Werling, A.M.; Walitza, S.; Grünblatt, E. The stress-Wnt-signaling axis: A hypothesis for attention-deficit hyperactivity disorder and therapy approaches. *Transl. Psychiatry,* **2020**, *10*(1), 315. http://dx.doi.org/10.1038/s41398-020-00999-9 PMID: 32948744

[38] Aebi, M.; van Donkelaar, M.M.; Poelmans, G.; Buitelaar, J.K.; Sonuga-Barke, E.J.; Stringaris, A.; Consortium, I.; Faraone, S.V.; Franke, B.; Steinhausen, H.C.; van Hulzen, K.J. Gene-set and multivariate genome-wide association analysis of oppositional defiant behavior subtypes in attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet.,* **2016**, *171*(5), 573-588. http://dx.doi.org/10.1002/ajmg.b.32346 PMID: 26184070

[39] Stergiakouli, E.; Hamshere, M.; Holmans, P.; Langley, K.; Zaharieva, I.; Hawi, Z.; Kent, L.; Gill, M.; Williams, N.; Owen, M.J.; O'Donovan, M.; Thapar, A. Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. *Am. J. Psychiatry,* **2012**, *169*(2), 186-194. http://dx.doi.org/10.1176/appi.ajp.2011.11040551 PMID: 22420046

[40] Williams, N.M.; Franke, B.; Mick, E.; Anney, R.J.; Freitag, C.M.; Gill, M.; Thapar, A.; O'Donovan, M.C.; Owen, M.J.; Holmans, P.; Kent, L.; Middleton, F.; Zhang-James, Y.; Liu, L.; Meyer, J.; Nguyen, T.T.; Romanos, J.; Romanos, M.; Seitz, C.; Renner, T.J.; Walitza, S.; Warnke, A.; Palmason, H.; Buitelaar, J.; Rommelse, N.; Vasquez, A.A.; Hawi, Z.; Langley, K.; Sergeant, J.; Steinhausen, H.C.; Roeyers, H.; Biederman, J.; Zaharieva, I.; Hakonarson, H.; Elia, J.; Lionel, A.C.; Crosbie, J.; Marshall, C.R.; Schachar, R.; Scherer, S.W.; Todorov, A.; Smalley, S.L.; Loo, S.; Nelson, S.; Shtir, C.; Asherson, P.; Reif, A.; Lesch, K.P.; Faraone, S.V. Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: The role of rare variants and duplications at 15q13.3. *Am. J. Psychiatry,* **2012**, *169*(2), 195-204. http://dx.doi.org/10.1176/appi.ajp.2011.11060822 PMID: 22420048

[41] Thapar, A. Discoveries on the genetics of ADHD in the 21st century: New findings and their implications. *Am. J. Psychiatry,* **2018**, *175*(10), 943-950. http://dx.doi.org/10.1176/appi.ajp.2018.18040383 PMID: 30111187

[42] Demontis, D.; Walters, R.K.; Martin, J.; Mattheisen, M.; Als, T.D.; Agerbo, E.; Baldursson, G.; Belliveau, R.; Bybjerg-Grauholm, J.; Bækvad-Hansen, M.; Cerrato, F.; Chambert, K.; Churchhouse, C.; Dumont, A.; Eriksson, N.; Gandal, M.; Goldstein, J.I.; Grasby, K.L.; Grove, J.; Gudmundsson, O.O.; Hansen, C.S.; Hauberg, M.E.; Hollegaard, M.V.; Howrigan, D.P.; Huang, H.; Maller, J.B.; Martin, A.R.; Martin, N.G.; Moran, J.; Pallesen, J.; Palmer, D.S.; Pedersen, C.B.; Pedersen, M.G.; Poterba, T.; Poulsen, J.B.; Ripke, S.; Robinson, E.B.; Satterstrom, F.K.; Stefansson, H.; Stevens, C.; Turley, P.; Walters, G.B.; Won, H.; Wright, M.J.; Andreassen, O.A.; Asherson, P.; Burton, C.L.; Boomsma, D.I.; Cormand, B.; Dalsgaard, S.; Franke, B.; Gelernter, J.; Geschwind, D.; Hakonarson, H.; Haavik, J.; Kranzler, H.R.; Kuntsi, J.; Langley, K.; Lesch, K.P.; Middeldorp, C.; Reif, A.; Rohde, L.A.; Roussos, P.; Schachar, R.; Sklar, P.; Sonuga-Barke, E.J.S.; Sullivan, P.F.; Thapar, A.; Tung, J.Y.; Waldman, I.D.; Medland, S.E.; Stefansson, K.; Nordentoft, M.; Hougaard, D.M.; Werge, T.; Mors, O.; Mortensen, P.B.; Daly, M.J.; Faraone, S.V.; Børglum, A.D.; Neale, B.M. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat. Genet.,* **2019**, *51*(1), 63-75. http://dx.doi.org/10.1038/s41588-018-0269-7 PMID: 30478444

[43] Pirdehghan, A.; Aghakoochak, A.; Karimi, M.; Kazemi, L. Relation between low birth weight with attention deficit and hyper activity disorder in children. *Majallah-i Danishgah-i Ulum-i Pizishki-i Gurgan,* **2015**, *17*(2)

[44] Driga, A-M.; Drigas, A. ADHD in the early years: Pre-natal and early causes and alternative ways of dealing. *Int. J. Online Biomed. Engin.,* **2019**, *15*(13). http://dx.doi.org/10.3991/ijoe.v15i13.11203

[45] Chu, S-M.; Tsai, M-H.; Hwang, F-M.; Hsu, J-F.; Huang, H.R.; Huang, Y-S. The relationship between attention deficit hyperactivity disorder and premature infants in Taiwanese: A case control study. *BMC Psychiatry,* **2012**, *12*(1), 85. http://dx.doi.org/10.1186/1471-244X-12-85 PMID: 22824325

[46] Nasrollahzadeh Masoomian, M.; Asadollahi, Z.; Sepehri, F.; Fatehi, A.; Salehi Shahrbabaki, M.H.; Bidaki, R. The relationship between attention deficit/hyperactivity and immaturity in children ages 13-7 years old referring to health centers in the city of rafsanjan in 1392. *Studies in Medical Sciences,* **2016**, *27*(6), 515-522.

[47] Wallis, D.; Russell, H.F.; Muenke, M. Review: Genetics of attention deficit/hyperactivity disorder. *J. Pediatr. Psychol.,* **2008**, *33*(10), 1085-1099. http://dx.doi.org/10.1093/jpepsy/jsn049 PMID: 18522996

[48] Millichap, J.G.; Yee, M.M. The diet factor in attention-deficit/hyperactivity disorder. *Pediatrics,* **2012**, *129*(2), 330-337. http://dx.doi.org/10.1542/peds.2011-2199 PMID: 22232312

[49] Cormier, E.; Elder, J.H. Diet and child behavior problems: Fact or fiction? *Pediatr. Nurs.,* **2007**, *33*(2), 138-143. PMID: 17542236

[50] Ozlem, E. What causes ADHD. *AAP Grand Rounds,* **2012**, *27*(6), 72. http://dx.doi.org/10.1542/gr.27-6-72

[51] Peterson, B.S.; Rauh, V.A.; Bansal, R.; Hao, X.; Toth, Z.; Nati, G.; Walsh, K.; Miller, R.L.; Arias, F.; Semanek, D.; Perera, F. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. *JAMA Psychiatry,* **2015**, *72*(6), 531-540. http://dx.doi.org/10.1001/jamapsychiatry.2015.57 PMID: 25807066

[52] Hong, S-B.; Im, M.H.; Kim, J.W.; Park, E.J.; Shin, M.S.; Kim, B.N.; Yoo, H.J.; Cho, I.H.; Bhang, S.Y.; Hong, Y.C.; Cho, S.C. Environmental lead exposure and attention deficit/hyperactivity disorder symptom domains in a community sample of South Korean school-age children. *Environ. Health Perspect.,* **2015**, *123*(3), 271-276. http://dx.doi.org/10.1289/ehp.1307420 PMID: 25280233

[53] Biederman, J.; Faraone, S.V. Attention-deficit hyperactivity disorder. *Lancet,* **2005**, *366*(9481), 237-248. http://dx.doi.org/10.1016/S0140-6736(05)66915-2 PMID: 16023516

[54] Elbaz, F.; Zahra, S.; Hanafy, H. Magnesium, zinc and copper estimation in children with attention deficit hyperactivity disorder (ADHD). *Egypt. J. Med. Hum. Genet.,* **2017**, *18*(2), 153-163. http://dx.doi.org/10.1016/j.ejmhg.2016.04.009

[55] Wang, Y.; Huang, L.; Zhang, L.; Qu, Y.; Mu, D. Iron status in attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *PLoS One,* **2017**, *12*(1), e0169145. http://dx.doi.org/10.1371/journal.pone.0169145 PMID: 28046016

[56] Huang, Y-H.; Zeng, B-Y.; Li, D-J.; Cheng, Y-S.; Chen, T-Y.; Liang, H-Y.; Yang, W-C.; Lin, P-Y.; Chen, Y-W.; Tseng, P-T.; Lin, C.H. Significantly lower serum and hair magnesium levels in children with attention deficit hyperactivity disorder than controls: A systematic review and meta-analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2019**, *90*, 134-141. http://dx.doi.org/10.1016/j.pnpbp.2018.11.012 PMID: 30496768

[57] Cornu, C.; Mercier, C.; Ginhoux, T.; Masson, S.; Mouchet, J.; Nony, P.; Kassai, B.; Laudy, V.; Berquin, P.; Franc, N.; Le Heuzey, M.F.; Desombre, H.; Revol, O. A double-blind placebo-controlled randomised trial of omega-3 supplementation in children with moderate ADHD symptoms. *Eur. Child Adolesc. Psychiatry,* **2018**, *27*(3), 377-384. http://dx.doi.org/10.1007/s00787-017-1058-z PMID: 28993963

[58] San Mauro Martín, I.; Blumenfeld Olivares, J.A.; Garicano Vilar, E.; Echeverry López, M.; García Bernat, M.; Quevedo Santos, Y.; Blanco López, M.; Elortegui Pascual, P.; Borregon Rivilla, E.; Rincón Barrado, M. Nutritional and environmental factors in attention-deficit hyperactivity disorder (ADHD): A cross-sectional study. *Nutr. Neurosci.,* **2018**, *21*(9), 641-647. http://dx.doi.org/10.1080/1028415X.2017.1331952 PMID: 28602133

[59] Heilskov Rytter, M.J.; Andersen, L.B.B.; Houmann, T.; Bilenberg, N.; Hvolby, A.; Mølgaard, C.; Michaelsen, K.F.; Lauritzen, L. Diet in the treatment of ADHD in children - a systematic review of the literature. *Nord. J. Psychiatry,* **2015**, *69*(1), 1-18. http://dx.doi.org/10.3109/08039488.2014.921933 PMID: 24934907

[60] Borge, T.C.; Biele, G.; Papadopoulou, E.; Andersen, L.F.; Jacka, F.; Eggesbø, M.; Caspersen, I.H.; Aase, H.; Meltzer, H.M.;

Brantsæter, A.L. The associations between maternal and child diet quality and child ADHD - findings from a large Norwegian pregnancy cohort study. *BMC Psychiatry,* **2021**, *21*(1), 139. http://dx.doi.org/10.1186/s12888-021-03130-4 PMID: 33685413

[61] Sonuga-Barke, E.J.; Brandeis, D.; Cortese, S.; Daley, D.; Ferrin, M.; Holtmann, M.; Stevenson, J.; Danckaerts, M.; van der Oord, S.; Döpfner, M.; Dittmann, R.W.; Simonoff, E.; Zuddas, A.; Banaschewski, T.; Buitelaar, J.; Coghill, D.; Hollis, C.; Konofal, E.; Lecendreux, M.; Wong, I.C.; Sergeant, J. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am. J. Psychiatry,* **2013**, *170*(3), 275-289. http://dx.doi.org/10.1176/appi.ajp.2012.12070991 PMID: 23360949

[62] Lange, K.W.; Hauser, J.; Lange, K.M.; Makulska-Gertruda, E.; Nakamura, Y.; Reissmann, A.; Sakaue, Y.; Takano, T.; Takeuchi, Y. The role of nutritional supplements in the treatment of ADHD: what the evidence says. *Curr. Psychiatry Rep.,* **2017**, *19*(2), 8. http://dx.doi.org/10.1007/s11920-017-0762-1 PMID: 28168597

[63] Tanriover, G.; Seval-Celik, Y.; Ozsoy, O.; Akkoyunlu, G.; Savcioglu, F.; Hacioglu, G.; Demir, N.; Agar, A. The effects of docosahexaenoic acid on glial derived neurotrophic factor and neurturin in bilateral rat model of Parkinson's disease. *Folia Histochem. Cytobiol.,* **2010**, *48*(3), 434-441. http://dx.doi.org/10.2478/v10042-010-0047-6 PMID: 21071351

[64] Yan, Y.; Jiang, W.; Spinetti, T.; Tardivel, A.; Castillo, R.; Bourquin, C.; Guarda, G.; Tian, Z.; Tschopp, J.; Zhou, R. Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. *Immunity,* **2013**, *38*(6), 1154-1163. http://dx.doi.org/10.1016/j.immuni.2013.05.015 PMID: 23809162

[65] Robertson, R.C.; Seira Oriach, C.; Murphy, K.; Moloney, G.M.; Cryan, J.F.; Dinan, T.G.; Paul Ross, R.; Stanton, C. Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain Behav. Immun.,* **2017**, *59*, 21-37. http://dx.doi.org/10.1016/j.bbi.2016.07.145 PMID: 27423492

[66] Very, N.; Vercoutter-Edouart, A.S.; Lefebvre, T.; Hardivillé, S.; El Yazidi-Belkoura, I. Cross-dysregulation of O-GlcNAcylation and PI3K/Akt/mTOR axis in human chronic diseases. *Front. Endocrinol. (Lausanne),* **2018**, *9*, 602. http://dx.doi.org/10.3389/fendo.2018.00602 PMID: 30356686

[67] Jean, S.; Kiger, A.A. Classes of phosphoinositide 3-kinases at a glance. *J. Cell Sci.,* **2014**, *127*(Pt 5), 923-928. http://dx.doi.org/10.1242/jcs.093773 PMID: 24587488

[68] Kriplani, N.; Hermida, M.A.; Brown, E.R.; Leslie, N.R.; Class, I. Class I PI 3-kinases: Function and evolution. *Adv. Biol. Regul.,* **2015**, *59*, 53-64. http://dx.doi.org/10.1016/j.jbior.2015.05.002 PMID: 26159297

[69] Maffei, A.; Lembo, G.; Carnevale, D. PI3Kinases in Diabetes Mellitus and Its Related Complications. *Int. J. Mol. Sci.,* **2018**, *19*(12), 4098. http://dx.doi.org/10.3390/ijms19124098 PMID: 30567315

[70] Falasca, M.; Maffucci, T. Regulation and cellular functions of class II phosphoinositide 3-kinases. *Biochem. J.,* **2012**, *443*(3), 587-601. http://dx.doi.org/10.1042/BJ20120008 PMID: 22507127

[71] Devereaux, K.; Dall'Armi, C.; Alcazar-Roman, A.; Ogasawara, Y.; Zhou, X.; Wang, F.; Yamamoto, A.; De Camilli, P.; Di Paolo, G. Regulation of mammalian autophagy by class II and III PI 3-kinases through PI3P synthesis. *PLoS One,* **2013**, *8*(10), e76405. http://dx.doi.org/10.1371/journal.pone.0076405 PMID: 24098492

[72] Burke, J.E.; Williams, R.L. Synergy in activating class I PI3Ks. *Trends Biochem. Sci.,* **2015**, *40*(2), 88-100. http://dx.doi.org/10.1016/j.tibs.2014.12.003 PMID: 25573003

[73] Leevers, S.J.; Vanhaesebroeck, B.; Waterfield, M.D. Signalling through phosphoinositide 3-kinases: the lipids take centre stage. *Curr. Opin. Cell Biol.,* **1999**, *11*(2), 219-225. http://dx.doi.org/10.1016/S0955-0674(99)80029-5 PMID: 10209156

[74] Posor, Y.; Eichhorn-Grünig, M.; Haucke, V. Phosphoinositides in endocytosis. *Biochimica Et Biophysica Acta (BBA)-. Mol. Cell Biol. Lipids,* **2015**, *1851*(6), 794-804. http://dx.doi.org/10.1016/j.bbalip.2014.09.014

[75] Leslie, N.R. The redox regulation of PI 3-kinase-dependent signaling. *Antioxid. Redox Signal.,* **2006**, *8*(9-10), 1765-1774. http://dx.doi.org/10.1089/ars.2006.8.1765 PMID: 16987030

[76] Zhang, Y.; Du, Y.; Le, W.; Wang, K.; Kieffer, N.; Zhang, J. Redox control of the survival of healthy and diseased cells. *Antioxid. Redox Signal.,* **2011**, *15*(11), 2867-2908. http://dx.doi.org/10.1089/ars.2010.3685 PMID: 21457107

[77] Fruman, D.A.; Chiu, H.; Hopkins, B.D.; Bagrodia, S.; Cantley, L.C.; Abraham, R.T. The PI3K pathway in human disease. *Cell,* **2017**, *170*(4), 605-635. http://dx.doi.org/10.1016/j.cell.2017.07.029 PMID: 28802037

[78] Chen, S-P.; Zhou, Y-Q.; Liu, D-Q.; Zhang, W.; Manyande, A.; Guan, X-H.; Tian, Y.K.; Ye, D-W.; Omar, D.M. PI3K/Akt pathway: a potential therapeutic target for chronic pain. *Curr. Pharm. Des.,* **2017**, *23*(12), 1860-1868. http://dx.doi.org/10.2174/1381612823666170210150147 PMID: 28190392

[79] Wang, D.; Zhou, W.; Chen, J.; Wei, W. Upstream regulators of phosphoinositide 3-kinase and their role in diseases. *J. Cell. Physiol.,* **2019**. http://dx.doi.org/10.1002/jcp.28215 PMID: 30710358

[80] Shih, M-H.; Kao, S-C.; Wang, W.; Yaster, M.; Tao, Y-X. Spinal cord NMDA receptor-mediated activation of mammalian target of rapamycin is required for the development and maintenance of bone cancer-induced pain hypersensitivities in rats. *J. Pain,* **2012**, *13*(4), 338-349. http://dx.doi.org/10.1016/j.jpain.2011.12.006 PMID: 22341316

[81] Cunha, T.M.; Roman-Campos, D.; Lotufo, C.M.; Duarte, H.L.; Souza, G.R.; Verri, W.A., Jr; Funez, M.I.; Dias, Q.M.; Schivo, I.R.; Domingues, A.C.; Sachs, D.; Chiavegatto, S.; Teixeira, M.M.; Hothersall, J.S.; Cruz, J.S.; Cunha, F.Q.; Ferreira, S.H. Morphine peripheral analgesia depends on activation of the PI3Kgamma/AKT/nNOS/NO/KATP signaling pathway. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(9), 4442-4447. http://dx.doi.org/10.1073/pnas.0914733107 PMID: 20147620

[82] Guan, X.; Fu, Q.; Xiong, B.; Song, Z.; Shu, B.; Bu, H.; Xu, B.; Manyande, A.; Cao, F.; Tian, Y. Activation of PI3Kγ/Akt pathway mediates bone cancer pain in rats. *J. Neurochem.,* **2015**, *134*(3), 590-600. http://dx.doi.org/10.1111/jnc.13139 PMID: 25919859

[83] Houslay, D.M.; Anderson, K.E.; Chessa, T.; Kulkarni, S.; Fritsch, R.; Downward, J.; Backer, J.M.; Stephens, L.R.; Hawkins, P.T. Coincident signals from GPCRs and receptor tyrosine kinases are uniquely transduced by PI3Kβ in myeloid cells. *Sci. Signal.,* **2016**, *9*(441), ra82-ra82. http://dx.doi.org/10.1126/scisignal.aae0453 PMID: 27531651

[84] Huang, W.; Zhao, Y.; Zhu, X.; Cai, Z.; Wang, S.; Yao, S.; Qi, Z.; Xie, P. Fluoxetine upregulates phosphorylated-AKT and phosphorylated-ERK1/2 proteins in neural stem cells: evidence for a cross-talk between AKT and ERK1/2 pathways. *J. Mol. Neurosci.,* **2013**, *49*(2), 244-249. http://dx.doi.org/10.1007/s12031-012-9822-5 PMID: 22674052

[85] Hong, S-K.; Jeong, J.H.; Chan, A.M.; Park, J-I. AKT upregulates B-Raf Ser445 phosphorylation and ERK1/2 activation in prostate cancer cells in response to androgen depletion. *Exp. Cell Res.,* **2013**, *319*(12), 1732-1743. http://dx.doi.org/10.1016/j.yexcr.2013.05.008 PMID: 23701950

[86] Bonnas, C.; Specht, K.; Spleiss, O.; Froehner, S.; Dietmann, G.; Krüger, J.M.; Arbogast, S.; Feuerhake, F. Effects of cold ischemia and inflammatory tumor microenvironment on detection of PI3K/AKT and MAPK pathway activation patterns in clinical cancer samples. *Int. J. Cancer,* **2012**, *131*(7), 1621-1632. http://dx.doi.org/10.1002/ijc.27422 PMID: 22213219

[87] Lien, E.C.; Lyssiotis, C.A.; Cantley, L.C. Metabolic reprogramming by the PI3K-Akt-mTOR pathway in cancer. *Metabol. Cancer*; Springer, **2016**, pp. 39-72. http://dx.doi.org/10.1007/978-3-319-42118-6_3

[88] Koundouros, N.; Poulogiannis, G. Phosphoinositide 3-kinase/Akt signaling and redox metabolism in cancer. *Front. Oncol.,* **2018**, *8*, 160. http://dx.doi.org/10.3389/fonc.2018.00160 PMID: 29868481

[89] Lawrence, M.S.; Stojanov, P.; Mermel, C.H.; Robinson, J.T.; Garraway, L.A.; Golub, T.R.; Meyerson, M.; Gabriel, S.B.; Lander,

E.S.; Getz, G. Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature,* **2014**, *505*(7484), 495-501. http://dx.doi.org/10.1038/nature12912 PMID: 24390350

[90] Engelman, J.A.; Luo, J.; Cantley, L.C. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat. Rev. Genet.,* **2006**, *7*(8), 606-619. http://dx.doi.org/10.1038/nrg1879 PMID: 16847462

[91] Manning, B.D.; Toker, A. AKT/PKB signaling: navigating the network. *Cell,* **2017**, *169*(3), 381-405. http://dx.doi.org/10.1016/j.cell.2017.04.001 PMID: 28431241

[92] Brunet, A.; Datta, S.R.; Greenberg, M.E. Transcription-dependent and -independent control of neuronal survival by the PI3K-Akt signaling pathway. *Curr. Opin. Neurobiol.,* **2001**, *11*(3), 297-305. http://dx.doi.org/10.1016/S0959-4388(00)00211-7 PMID: 11399427

[93] Jacinto, E.; Facchinetti, V.; Liu, D.; Soto, N.; Wei, S.; Jung, S.Y.; Huang, Q.; Qin, J.; Su, B. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. *Cell,* **2006**, *127*(1), 125-137. http://dx.doi.org/10.1016/j.cell.2006.08.033 PMID: 16962653

[94] Thomas, G.V.; Tran, C.; Mellinghoff, I.K.; Welsbie, D.S.; Chan, E.; Fueger, B.; Czernin, J.; Sawyers, C.L. Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat. Med.,* **2006**, *12*(1), 122-127. http://dx.doi.org/10.1038/nm1337 PMID: 16341243

[95] Wang, H.; Deng, X.; Zhang, J.; Ou, Z.; Mai, J.; Ding, S.; Huo, S. Elevated expression of zinc finger protein 703 promotes cell proliferation and metastasis through PI3K/AKT/GSK-3β signalling in oral squamous cell carcinoma. *Cell. Physiol. Biochem.,* **2017**, *44*(3), 920-934. http://dx.doi.org/10.1159/000485360 PMID: 29176314

[96] Horwood, J.M.; Dufour, F.; Laroche, S.; Davis, S. Signalling mechanisms mediated by the phosphoinositide 3-kinase/Akt cascade in synaptic plasticity and memory in the rat. *Eur. J. Neurosci.,* **2006**, *23*(12), 3375-3384. http://dx.doi.org/10.1111/j.1460-9568.2006.04859.x PMID: 16820027

[97] Kocsis, K.; Frank, R.; Szabó, J.; Knapp, L.; Kis, Z.; Farkas, T.; Vécsei, L.; Toldi, J. Acetyl-l-carnitine restores synaptic transmission and enhances the inducibility of stable LTP after oxygen-glucose deprivation. *Neuroscience,* **2016**, *332*, 203-211. http://dx.doi.org/10.1016/j.neuroscience.2016.06.046 PMID: 27378558

[98] Saxton, R.A.; Sabatini, D.M. mTOR signaling in growth, metabolism, and disease. *Cell,* **2017**, *168*(6), 960-976. http://dx.doi.org/10.1016/j.cell.2017.02.004 PMID: 28283069

[99] Dibble, C.C.; Cantley, L.C. Regulation of mTORC1 by PI3K signaling. *Trends Cell Biol.,* **2015**, *25*(9), 545-555. http://dx.doi.org/10.1016/j.tcb.2015.06.002 PMID: 26159692

[100] Magnuson, B.; Ekim, B.; Fingar, D.C. Regulation and function of ribosomal protein S6 kinase (S6K) within mTOR signalling networks. *Biochem. J.,* **2012**, *441*(1), 1-21. http://dx.doi.org/10.1042/BJ20110892 PMID: 22168436

[101] Malka-Mahieu, H.; Newman, M.; Désaubry, L.; Robert, C.; Vagner, S. Molecular pathways: the eIF4F translation initiation complex—new opportunities for cancer treatment. *Clin. Cancer Res.,* **2017**, *23*(1), 21-25. http://dx.doi.org/10.1158/1078-0432.CCR-14-2362 PMID: 27789529

[102] Bruhn, M.A.; Pearson, R.B.; Hannan, R.D.; Sheppard, K.E. AKT-independent PI3-K signaling in cancer - emerging role for SGK3. *Cancer Manag. Res.,* **2013**, *5*, 281-292. PMID: 24009430

[103] Sohn, J-W.; Oh, Y.; Kim, K.W.; Lee, S.; Williams, K.W.; Elmquist, J.K. Leptin and insulin engage specific PI3K subunits in hypothalamic SF1 neurons. *Mol. Metab.,* **2016**, *5*(8), 669-679. http://dx.doi.org/10.1016/j.molmet.2016.06.004 PMID: 27656404

[104] Troutman, T.D.; Bazan, J.F.; Pasare, C. Toll-like receptors, signaling adapters and regulation of the pro-inflammatory response by PI3K. *Cell Cycle,* **2012**, *11*(19), 3559-3567. http://dx.doi.org/10.4161/cc.21572 PMID: 22895011

[105] Aksoy, E.; Taboubi, S.; Torres, D.; Delbauve, S.; Hachani, A.; Whitehead, M.A.; Pearce, W.P.; Berenjeno, I.M.; Nock, G.; Filloux, A.; Beyaert, R.; Flamand, V.; Vanhaesebroeck, B. The p110δ isoform of the kinase PI(3)K controls the subcellular compartmentalization of TLR4 signaling and protects from endotoxic shock. *Nat. Immunol.,* **2012**, *13*(11), 1045-1054. http://dx.doi.org/10.1038/ni.2426 PMID: 23023391

[106] Saponaro, C.; Cianciulli, A.; Calvello, R.; Dragone, T.; Iacobazzi, F.; Panaro, M.A. The PI3K/Akt pathway is required for LPS activation of microglial cells. *Immunopharmacol. Immunotoxicol.,* **2012**, *34*(5), 858-865. http://dx.doi.org/10.3109/08923973.2012.665461 PMID: 22397361

[107] Zhao, M.; Zhou, A.; Xu, L.; Zhang, X. The role of TLR4-mediated PTEN/PI3K/AKT/NF-κB signaling pathway in neuroinflammation in hippocampal neurons. *Neuroscience,* **2014**, *269*, 93-101. http://dx.doi.org/10.1016/j.neuroscience.2014.03.039 PMID: 24680857

[108] Kim, W-K.; Hwang, S-Y.; Oh, E-S.; Piao, H.Z.; Kim, K-W.; Han, I-O. TGF-β1 represses activation and resultant death of microglia *via* inhibition of phosphatidylinositol 3-kinase activity. *J. Immunol.,* **2004**, *172*(11), 7015-7023. http://dx.doi.org/10.4049/jimmunol.172.11.7015 PMID: 15153523

[109] Koh, S-H.; Park, H-H. Neurogenesis in stroke recovery. *Transl. Stroke Res.,* **2017**, *8*(1), 3-13. http://dx.doi.org/10.1007/s12975-016-0460-z PMID: 26987852

[110] Gonzalez-Perez, O. Neural stem cells in the adult human brain. *Biol. Biomed. Rep.,* **2012**, *2*(1), 59-69. PMID: 23181200

[111] Koh, S-H.; Lo, E.H. The role of the PI3K pathway in the regeneration of the damaged brain by neural stem cells after cerebral infarction. *J. Clin. Neurol.,* **2015**, *11*(4), 297-304. http://dx.doi.org/10.3988/jcn.2015.11.4.297 PMID: 26320845

[112] Rivière, J-B.; Mirzaa, G.M.; O'Roak, B.J.; Beddaoui, M.; Alcantara, D.; Conway, R.L.; St-Onge, J.; Schwartzentruber, J.A.; Gripp, K.W.; Nikkel, S.M.; Worthylake, T.; Sullivan, C.T.; Ward, T.R.; Butler, H.E.; Kramer, N.A.; Albrecht, B.; Armour, C.M.; Armstrong, L.; Caluseriu, O.; Cytrynbaum, C.; Drolet, B.A.; Innes, A.M.; Lauzon, J.L.; Lin, A.E.; Mancini, G.M.; Meschino, W.S.; Reggin, J.D.; Saggar, A.K.; Lerman-Sagie, T.; Uyanik, G.; Weksberg, R.; Zirn, B.; Beaulieu, C.L.; Majewski, J.; Bulman, D.E.; O'Driscoll, M.; Shendure, J.; Graham, J.M., Jr; Boycott, K.M.; Dobyns, W.B. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat. Genet.,* **2012**, *44*(8), 934-940. http://dx.doi.org/10.1038/ng.2331 PMID: 22729224

[113] Jansen, L.A.; Mirzaa, G.M.; Ishak, G.E.; O'Roak, B.J.; Hiatt, J.B.; Roden, W.H.; Gunter, S.A.; Christian, S.L.; Collins, S.; Adams, C.; Rivière, J.B.; St-Onge, J.; Ojemann, J.G.; Shendure, J.; Hevner, R.F.; Dobyns, W.B. PI3K/AKT pathway mutations cause a spectrum of brain malformations from megalencephaly to focal cortical dysplasia. *Brain,* **2015**, *138*(Pt 6), 1613-1628. http://dx.doi.org/10.1093/brain/awv045 PMID: 25722288

[114] Xiao, Z.; Peng, J.; Yang, L.; Kong, H.; Yin, F. Interleukin-1β plays a role in the pathogenesis of mesial temporal lobe epilepsy through the PI3K/Akt/mTOR signaling pathway in hippocampal neurons. *J. Neuroimmunol.,* **2015**, *282*, 110-117. http://dx.doi.org/10.1016/j.jneuroim.2015.04.003 PMID: 25903737

[115] Brandt, C.; Hillmann, P.; Noack, A.; Römermann, K.; Öhler, L.A.; Rageot, D.; Beaufils, F.; Melone, A.; Sele, A.M.; Wymann, M.P.; Fabbro, D.; Löscher, W. The novel, catalytic mTORC1/2 inhibitor PQR620 and the PI3K/mTORC1/2 inhibitor PQR530 effectively cross the blood-brain barrier and increase seizure threshold in a mouse model of chronic epilepsy. *Neuropharmacology,* **2018**, *140*, 107-120. http://dx.doi.org/10.1016/j.neuropharm.2018.08.002 PMID: 30081001

[116] Heras-Sandoval, D.; Pérez-Rojas, J.M.; Hernández-Damián, J.; Pedraza-Chaverri, J. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. *Cell. Signal.,* **2014**, *26*(12), 2694-2701. http://dx.doi.org/10.1016/j.cellsig.2014.08.019 PMID: 25173700

[117] Yang, L.; Wang, H.; Liu, L.; Xie, A. The role of insulin/IGF-1/PI3K/Akt/GSK3β signaling in Parkinson's disease dementia. *Front. Neurosci.,* **2018**, *12*, 73. http://dx.doi.org/10.3389/fnins.2018.00073 PMID: 29515352

[118] Li, S.; Chen, X.; Mao, L.; Zahid, K.R.; Wen, J.; Zhang, L.; Zhang, M.; Duan, J.; Duan, J.; Yin, X.; Wang, Y.; Zhao, L.; Tang, X.;

Wang, X.; Xu, G. Histone deacetylase 1 promotes glioblastoma cell proliferation and invasion *via* activation of PI3K/AKT and MEK/ERK signaling pathways. *Brain Res.,* **2018**, *1692*, 154-162. http://dx.doi.org/10.1016/j.brainres.2018.05.023 PMID: 29782850

[119] Daniel, P.M.; Filiz, G.; Brown, D.V.; Christie, M.; Waring, P.M.; Zhang, Y.; Haynes, J.M.; Pouton, C.; Flanagan, D.; Vincan, E.; Johns, T.G.; Montgomery, K.; Phillips, W.A.; Mantamadiotis, T. PI3K activation in neural stem cells drives tumorigenesis which can be ameliorated by targeting the cAMP response element binding protein. *Neuro-oncol.,* **2018**, *20*(10), 1344-1355. http://dx.doi.org/10.1093/neuonc/noy068 PMID: 29718345

[120] Seitz, C.; Hugle, M.; Cristofanon, S.; Tchoghandjian, A.; Fulda, S. The dual PI3K/mTOR inhibitor NVP-BEZ235 and chloroquine synergize to trigger apoptosis *via* mitochondrial-lysosomal cross-talk. *Int. J. Cancer,* **2013**, *132*(11), 2682-2693. http://dx.doi.org/10.1002/ijc.27935 PMID: 23151917

[121] Liu, Q.; Qiu, J.; Liang, M.; Golinski, J.; van Leyen, K.; Jung, J.E.; You, Z.; Lo, E.H.; Degterev, A.; Whalen, M.J. Akt and mTOR mediate programmed necrosis in neurons. *Cell Death Dis.,* **2014**, *5*(2), e1084-e1084. http://dx.doi.org/10.1038/cddis.2014.69 PMID: 24577082

[122] Ribeiro, M.; Rosenstock, T.R.; Oliveira, A.M.; Oliveira, C.R.; Rego, A.C. Insulin and IGF-1 improve mitochondrial function in a PI-3K/Akt-dependent manner and reduce mitochondrial generation of reactive oxygen species in Huntington's disease knock-in striatal cells. *Free Radic. Biol. Med.,* **2014**, *74*, 129-144. http://dx.doi.org/10.1016/j.freeradbiomed.2014.06.023 PMID: 24992836

[123] Kim, D.I.; Lee, K.H.; Gabr, A.A.; Choi, G.E.; Kim, J.S.; Ko, S.H.; Han, H.J. Aβ-Induced Drp1 phosphorylation through Akt activation promotes excessive mitochondrial fission leading to neuronal apoptosis. *Biochim. Biophys. Acta,* **2016**, *1863*(11), 2820-2834. http://dx.doi.org/10.1016/j.bbamcr.2016.09.003 PMID: 27599716

[124] Kilic, E.; Kilic, U.; Wang, Y.; Bassetti, C.L.; Marti, H.H.; Hermann, D.M. The phosphatidylinositol-3 kinase/Akt pathway mediates VEGF's neuroprotective activity and induces blood brain barrier permeability after focal cerebral ischemia. *FASEB J.,* **2006**, *20*(8), 1185-1187. http://dx.doi.org/10.1096/fj.05-4829fje PMID: 16641198

[125] Nguyen, N.; Lee, S.B.; Lee, Y.S.; Lee, K-H.; Ahn, J-Y. Neuroprotection by NGF and BDNF against neurotoxin-exerted apoptotic death in neural stem cells are mediated through Trk receptors, activating PI3-kinase and MAPK pathways. *Neurochem. Res.,* **2009**, *34*(5), 942-951. http://dx.doi.org/10.1007/s11064-008-9848-9 PMID: 18846424

[126] Ha, K-S.; Kim, K-M.; Kwon, Y-G.; Bai, S-K.; Nam, W-D.; Yoo, Y-M.; Kim, P.K.; Chung, H-T.; Billiar, T.R.; Kim, Y-M. Nitric oxide prevents 6-hydroxydopamine-induced apoptosis in PC12 cells through cGMP-dependent PI3 kinase/Akt activation. *FASEB J.,* **2003**, *17*(9), 1036-1047. http://dx.doi.org/10.1096/fj.02-0738com PMID: 12773486

[127] Namikawa, K.; Honma, M.; Abe, K.; Takeda, M.; Mansur, K.; Obata, T.; Miwa, A.; Okado, H.; Kiyama, H. Akt/protein kinase B prevents injury-induced motoneuron death and accelerates axonal regeneration. *J. Neurosci.,* **2000**, *20*(8), 2875-2886. http://dx.doi.org/10.1523/JNEUROSCI.20-08-02875.2000 PMID: 10751440

[128] Park, H-H.; Lee, K-Y.; Kim, S.H.; Lee, Y.J.; Koh, S-H. L-DOPA-induced neurotoxicity is reduced by the activation of the PI3K signaling pathway. *Toxicology,* **2009**, *265*(3), 80-86. http://dx.doi.org/10.1016/j.tox.2009.09.011 PMID: 19786063

[129] Zheng, R.; Zhang, Z-H.; Chen, C.; Chen, Y.; Jia, S-Z.; Liu, Q.; Ni, J-Z.; Song, G-L. Selenomethionine promoted hippocampal neurogenesis *via* the PI3K-Akt-GSK3β-Wnt pathway in a mouse model of Alzheimer's disease. *Biochem. Biophys. Res. Commun.,* **2017**, *485*(1), 6-15. http://dx.doi.org/10.1016/j.bbrc.2017.01.069 PMID: 28109879

[130] Huang, L.; Sherchan, P.; Wang, Y.; Reis, C.; Applegate, R.L., II; Tang, J.; Zhang, J.H. Phosphoinositide 3-kinase gamma contributes to neuroinflammation in a rat model of surgical brain injury. *J. Neurosci.,* **2015**, *35*(29), 10390-10401. http://dx.doi.org/10.1523/JNEUROSCI.0546-15.2015 PMID: 26203135

[131] Ribic, A.; Liu, X.; Crair, M.C.; Biederer, T. Structural organization and function of mouse photoreceptor ribbon synapses involve the immunoglobulin protein synaptic cell adhesion molecule 1. *J. Comp. Neurol.,* **2014**, *522*(4), 900-920. http://dx.doi.org/10.1002/cne.23452 PMID: 23982969

[132] Murakami, S.; Sakurai-Yageta, M.; Maruyama, T.; Murakami, Y. Trans-homophilic interaction of CADM1 activates PI3K by forming a complex with MAGuK-family proteins MPP3 and Dlg. *PLoS One,* **2014**, *9*(2), e82894. http://dx.doi.org/10.1371/journal.pone.0082894 PMID: 24503895

[133] Ugrumov, M.V. Non-dopaminergic neurons partly expressing dopaminergic phenotype: distribution in the brain, development and functional significance. *J. Chem. Neuroanat.,* **2009**, *38*(4), 241-256. http://dx.doi.org/10.1016/j.jchemneu.2009.08.004 PMID: 19698780

[134] Lute, B.J.; Khoshbouei, H.; Saunders, C.; Sen, N.; Lin, R.Z.; Javitch, J.A.; Galli, A. PI3K signaling supports amphetamine-induced dopamine efflux. *Biochem. Biophys. Res. Commun.,* **2008**, *372*(4), 656-661. http://dx.doi.org/10.1016/j.bbrc.2008.05.091 PMID: 18510945

[135] Bourque, M.; Liu, B.; Dluzen, D.E.; Di Paolo, T. Sex differences in methamphetamine toxicity in mice: effect on brain dopamine signaling pathways. *Psychoneuroendocrinology,* **2011**, *36*(7), 955-969. http://dx.doi.org/10.1016/j.psyneuen.2010.12.007 PMID: 21236583

[136] Carvelli, L.; Morón, J.A.; Kahlig, K.M.; Ferrer, J.V.; Sen, N.; Lechleiter, J.D.; Leeb-Lundberg, L.M.; Merrill, G.; Lafer, E.M.; Ballou, L.M.; Shippenberg, T.S.; Javitch, J.A.; Lin, R.Z.; Galli, A. PI 3-kinase regulation of dopamine uptake. *J. Neurochem.,* **2002**, *81*(4), 859-869. http://dx.doi.org/10.1046/j.1471-4159.2002.00892.x PMID: 12065645

[137] Weaver, S.A.; Ward, S.G. Phosphoinositide 3-kinases in the gut: a link between inflammation and cancer? *Trends Mol. Med.,* **2001**, *7*(10), 455-462. http://dx.doi.org/10.1016/S1471-4914(01)02107-4 PMID: 11597520

[138] Lv, T.; Wang, S-D.; Bai, J. Thioredoxin-1 was required for CREB activity by methamphetamine in rat pheochromocytoma cells. *Cell. Mol. Neurobiol.,* **2013**, *33*(3), 319-325. http://dx.doi.org/10.1007/s10571-012-9897-0 PMID: 23239345

[139] Hong, S-I.; Kim, M-J.; You, I-J.; Kwon, S-H.; Ma, S-X.; Hwang, J-Y.; Seo, J-Y.; Ko, Y-H.; Lee, B.R.; Lee, S-Y.; Jang, C-G. Phentermine induces conditioned rewarding effects *via* activation of the PI3K/Akt signaling pathway in the nucleus accumbens. *Psychopharmacology (Berl.),* **2016**, *233*(8), 1405-1413. http://dx.doi.org/10.1007/s00213-016-4231-z PMID: 26887589

[140] Ulke, C.; Rullmann, M.; Huang, J.; Luthardt, J.; Becker, G-A.; Patt, M.; Meyer, P.M.; Tiepolt, S.; Hesse, S.; Sabri, O.; Strauß, M. Adult attention-deficit/hyperactivity disorder is associated with reduced norepinephrine transporter availability in right attention networks: a (S,S)-O-[^{11}C]methylreboxetine positron emission tomography study. *Transl. Psychiatry,* **2019**, *9*(1), 301. http://dx.doi.org/10.1038/s41398-019-0619-y PMID: 31732713

[141] Sukmajaya, A.C.; Lusida, M.I.; Soetjipto, ; Setiawati, Y. Systematic review of gut microbiota and attention-deficit hyperactivity disorder (ADHD). *Ann. Gen. Psychiatry,* **2021**, *20*(1), 12. http://dx.doi.org/10.1186/s12991-021-00330-w PMID: 33593384

[142] Andersen, S.L. Changes in the second messenger cyclic AMP during development may underlie motoric symptoms in attention deficit/hyperactivity disorder (ADHD). *Behav. Brain Res.,* **2002**, *130*(1-2), 197-201. http://dx.doi.org/10.1016/S0166-4328(01)00417-X PMID: 11864735

[143] Fraporti, T.T.; Contini, V.; Tovo-Rodrigues, L.; Recamonde-Mendoza, M.; Rovaris, D.L.; Rohde, L.A.; Hutz, M.H.; Salatino-Oliveira, A.; Genro, J.P. Synergistic effects between ADORA2A and DRD2 genes on anxiety disorders in children with ADHD. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2019**, *93*, 214-220. http://dx.doi.org/10.1016/j.pnpbp.2019.03.021 PMID: 30946941

[144] Zhang, X.; Du, Q.; Yang, Y.; Wang, J.; Liu, Y.; Zhao, Z.; Zhu, Y.; Liu, C. Salidroside alleviates ischemic brain injury in mice with is-

chemic stroke through regulating BDNK mediated PI3K/Akt pathway. *Biochem. Pharmacol.,* **2018**, *156*, 99-108. http://dx.doi.org/10.1016/j.bcp.2018.08.015 PMID: 30114387

[145] Sun, H.; Wang, Z.; Sebastian Yakisich, J. Natural products targeting autophagy *via* the PI3K/Akt/mTOR pathway as anticancer agents. *Anticancer Agents Med Chem.,* **2013**, *13*(7), 1048-1056. http://dx.doi.org/10.2174/18715206113139990130 PMID: 23293890

[146] Funaya, N.; Haginaka, J. Matrine- and oxymatrine-imprinted monodisperse polymers prepared by precipitation polymerization and their applications for the selective extraction of matrine-type alkaloids from Sophora flavescens Aiton. *J. Chromatogr. A,* **2012**, *1248*, 18-23. http://dx.doi.org/10.1016/j.chroma.2012.05.081 PMID: 22695694

[147] Lan, X.; Zhao, J.; Zhang, Y.; Chen, Y.; Liu, Y.; Xu, F. Oxymatrine exerts organ- and tissue-protective effects by regulating inflammation, oxidative stress, apoptosis, and fibrosis: From bench to bedside. *Pharmacol. Res.,* **2020**, *151*, 104541. http://dx.doi.org/10.1016/j.phrs.2019.104541 PMID: 31733326

[148] Wu, B.; Yue, H.; Zhou, G.H.; Zhu, Y.Y.; Wu, T.H.; Wen, J.F.; Cho, K.W.; Jin, S.N. Protective effects of oxymatrine on homocysteine-induced endothelial injury: Involvement of mitochondria-dependent apoptosis and Akt-eNOS-NO signaling pathways. *Eur. J. Pharmacol.,* **2019**, *864*, 172717. http://dx.doi.org/10.1016/j.ejphar.2019.172717 PMID: 31586637

[149] Jiao-Yan, Y.; Qing-Qing, L.; Xi, L.; Mei, Z.; Ting, S.; Na, H.; Wei, J.; Rui-Tao, Z.; Peng, Y.; Qi, Y. Oxymatrine improves blood-brain barrier integrity after cerebral ischemia-reperfusion injury by downregulating CAV1 and MMP9 expression. *Phytomedicine,* **2021**, *84*, 153505. http://dx.doi.org/10.1016/j.phymed.2021.153505 PMID: 33626426

[150] Liu, Y.; Wang, H.; Liu, N.; Du, J.; Lan, X.; Qi, X.; Zhuang, C.; Sun, T.; Li, Y.; Yu, J. Oxymatrine protects neonatal rat against hypoxic-ischemic brain damage via PI3K/Akt/GSK3β pathway. *Life Sci.,* **2020**, *254*, 116444. http://dx.doi.org/10.1016/j.lfs.2019.04.070 PMID: 31102745

[151] Zhao, J.; Shi, Z.; Liu, S.; Li, J.; Huang, W. Ginsenosides Rg1 from Panax ginseng: a potential therapy for acute liver failure patients? *Evid Based Complement Alternat Med,* **2014**, *2014*, 538059. http://dx.doi.org/10.1155/2014/538059 PMID: 25431611

[152] Tu, L.; Wang, Y.; Chen, D.; Xiang, P.; Shen, J.; Li, Y.; Wang, S. Protective effects of notoginsenoside r1 via regulation of the pi3k-akt-mtor/jnk pathway in neonatal cerebral hypoxic–ischemic brain injury. *Neurochem. Res.,* **2018**, *43*(6), 1210-1226. http://dx.doi.org/10.1007/s11064-018-2538-3 PMID: 29696512

[153] AlQathama, A.; Prieto, J.M. Natural products with therapeutic potential in melanoma metastasis. *Nat. Prod. Rep.,* **2015**, *32*(8), 1170-1182. http://dx.doi.org/10.1039/C4NP00130C PMID: 26018751

[154] Ayaz, M.; Sadiq, A.; Junaid, M.; Ullah, F.; Ovais, M.; Ullah, I.; Ahmed, J.; Shahid, M. Flavonoids as prospective neuroprotectants and their therapeutic propensity in aging associated neurological disorders. *Front. Aging Neurosci.,* **2019**, *11*, 155. http://dx.doi.org/10.3389/fnagi.2019.00155 PMID: 31293414

[155] Chen, X.; Gu, N.; Xue, C.; Li, B.R. Plant flavonoid taxifolin inhibits the growth, migration and invasion of human osteosarcoma cells. *Mol. Med. Rep.,* **2018**, *17*(2), 3239-3245. PMID: 29257319

[156] Saito, S.; Tanaka, M.; Satoh-Asahara, N.; Carare, R.O.; Ihara, M. Taxifolin: a potential therapeutic agent for cerebral amyloid angiopathy. *Front. Pharmacol.,* **2021**, *12*, 643357. http://dx.doi.org/10.3389/fphar.2021.643357 PMID: 33643053

[157] Oi, N.; Chen, H.; Ok Kim, M.; Lubet, R.A.; Bode, A.M.; Dong, Z. Taxifolin suppresses UV-induced skin carcinogenesis by targeting EGFR and PI3K. *Cancer Prev. Res. (Phila.),* **2012**, *5*(9), 1103-1114. http://dx.doi.org/10.1158/1940-6207.CAPR-11-0397 PMID: 22805054

[158] He, M.; Min, J-W.; Kong, W-L.; He, X-H.; Li, J-X.; Peng, B-W. A review on the pharmacological effects of vitexin and isovitexin. *Fitoterapia,* **2016**, *115*, 74-85. http://dx.doi.org/10.1016/j.fitote.2016.09.011 PMID: 27693342

[159] Liu, X.; Jiang, Q.; Liu, H.; Luo, S. Vitexin induces apoptosis through mitochondrial pathway and PI3K/Akt/mTOR signaling in human non-small cell lung cancer A549 cells. *Biol. Res.,* **2019**, *52*(1), 7. http://dx.doi.org/10.1186/s40659-019-0214-y PMID: 30797236

[160] Ahn, J.; Ahn, H.S.; Cheong, J.H.; Peña, I.D. Natural product-derived treatments for attention-deficit/hyperactivity disorder: safety, efficacy, and therapeutic potential of combination therapy. *Neural Plast,* **2016**, *2016*, 1320423. http://dx.doi.org/10.1155/2016/1320423 PMID: 26966583

[161] Pham, H.T.N.; Tran, H.N.; Nguyen, P.T.; Le, X.T.; Nguyen, K.M.; Phan, S.V.; Yoneyama, M.; Ogita, K.; Yamaguchi, T.; Folk, W.R.; Yamaguchi, M.; Matsumoto, K. Bacopa monnieri (L.) Wettst. Extract improves memory performance via promotion of neurogenesis in the hippocampal dentate gyrus of adolescent mice. *Int. J. Mol. Sci.,* **2020**, *21*(9), 3365. http://dx.doi.org/10.3390/ijms21093365 PMID: 32397562

[162] Petcharat, K.; Singh, M.; Ingkaninan, K.; Attarat, J.; Yasothornsrikul, S. *Bacopa monnieri* protects SH-SY5Y cells against *tert*-Butyl hydroperoxide-induced cell death *via* the ERK and PI3K pathways. *Siriraj Med J.,* **2015**, *67*(1), 20-26. PMID: 29152617

[163] Le, X.T.; Nguyet Pham, H.T.; Van Nguyen, T.; Minh Nguyen, K.; Tanaka, K.; Fujiwara, H.; Matsumoto, K. Protective effects of Bacopa monnieri on ischemia-induced cognitive deficits in mice: the possible contribution of bacopaside I and underlying mechanism. *J. Ethnopharmacol.,* **2015**, *164*, 37-45. http://dx.doi.org/10.1016/j.jep.2015.01.041 PMID: 25660331

[164] Liu, P-K.; Weng, Z-M.; Ge, G-B.; Li, H-L.; Ding, L-L.; Dai, Z-R.; Hou, X-D.; Leng, Y-H.; Yu, Y.; Hou, J. Biflavones from Ginkgo biloba as novel pancreatic lipase inhibitors: Inhibition potentials and mechanism. *Int. J. Biol. Macromol.,* **2018**, *118*(Pt B), 2216-2223. http://dx.doi.org/10.1016/j.ijbiomac.2018.07.085 PMID: 30009906

[165] Lejri, I.; Grimm, A.; Eckert, A. Ginkgo biloba extract increases neurite outgrowth and activates the Akt/mTOR pathway. *PLoS One,* **2019**, *14*(12), e0225761. http://dx.doi.org/10.1371/journal.pone.0225761 PMID: 31790465

[166] Nada, S.E.; Shah, Z.A. Preconditioning with Ginkgo biloba (EGb 761®) provides neuroprotection through HO1 and CRMP2. *Neurobiol. Dis.,* **2012**, *46*(1), 180-189. http://dx.doi.org/10.1016/j.nbd.2012.01.006 PMID: 22297164

[167] Nada, S.E.; Tulsulkar, J.; Shah, Z.A. Heme oxygenase 1-mediated neurogenesis is enhanced by Ginkgo biloba (EGb 761®) after permanent ischemic stroke in mice. *Mol. Neurobiol.,* **2014**, *49*(2), 945-956. http://dx.doi.org/10.1007/s12035-013-8572-x PMID: 24154866

[168] Ong, W-Y.; Farooqui, T.; Koh, H-L.; Farooqui, A.A.; Ling, E-A. Protective effects of ginseng on neurological disorders. *Front. Aging Neurosci.,* **2015**, *7*, 129. http://dx.doi.org/10.3389/fnagi.2015.00129 PMID: 26236231

[169] Nguyen, C.T.; Luong, T.T.; Kim, G.-L.; Pyo, S.; Rhee, D.-K. Korean red ginseng inhibits apoptosis in neuroblastoma cells *via* estrogen receptor β-mediated phosphatidylinositol-3 kinase/Akt signaling. *J Ginseng Res,* **2015**, *39*(1), 69-75. http://dx.doi.org/10.1016/j.jgr.2014.06.005 PMID: 25535479

[170] Razlog, R.; Pellow, J.; White, S.J. A pilot study on the efficacy of Valeriana officinalis mother tincture and Valeriana officinalis 3X in the treatment of attention deficit hyperactivity disorder. *Health SA Gesondheid,* **2011**, *17*(1), 1-7.

[171] Pellow, J.; Solomon, E.M.; Barnard, C.N. Complementary and alternative medical therapies for children with attention-deficit/hyperactivity disorder (ADHD). *Altern. Med. Rev.,* **2011**, *16*(4), 323-337. PMID: 22214252

[172] Arnold, L.E.; Amato, A.; Bozzolo, H.; Hollway, J.; Cook, A.; Ramadan, Y.; Crowl, L.; Zhang, D.; Thompson, S.; Testa, G.; Kliewer, V.; Wigal, T.; McBurnett, K.; Manos, M. Acetyl-L-carnitine (ALC) in attention-deficit/hyperactivity disorder: a multisite, placebo-controlled pilot trial. *J. Child Adolesc. Psychopharmacol.,* **2007**, *17*(6), 791-802. http://dx.doi.org/10.1089/cap.2007.018 PMID: 18315451

[173] Zhang, L.; Ding, K.; Wang, H.; Wu, Y.; Xu, J. Traumatic brain injury-induced neuronal apoptosis is reduced through modulation of PI3K and autophagy pathways in mouse by FTY720. *Cell. Mol. Neurobiol.,* **2016**, *36*(1), 131-142.

http://dx.doi.org/10.1007/s10571-015-0227-1 PMID: 26099903

[174] Chu, S.; Chen, P.; Hsieh, Y.; Yu, C.; Lin, M.; Lin, Y.; Kuo, D. Involvement of hypothalamic PI3K-STAT3 signalling in regulating amphetamine-mediated appetite suppression. *Br. J. Pharmacol.,* **2014**, *171*, 3223-3233. http://dx.doi.org/10.1111/bph.12667 PMID: 24597972

[175] Joo, S.W.; Kim, H-W. Treatment of children and adolescents with attention deficit hyperactivity disorder and/or Tourette's disorder with clonidine extended release. *Psychiatry Investig.,* **2018**, *15*(1), 90-93. http://dx.doi.org/10.4306/pi.2018.15.1.90 PMID: 29422931

[176] Takenouchi, Y.; Tsuboi, K.; Ohsuka, K.; Nobe, K.; Ohtake, K.; Okamoto, Y.; Kasono, K. Chronic treatment with α-lipoic acid improves endothelium-dependent vasorelaxation of aortas in high-fat diet-fed mice. *Biol. Pharm. Bull.,* **2019**, *42*(9), 1456-1463. http://dx.doi.org/10.1248/bpb.b18-00800 PMID: 31474707

[177] Tandel, H.; Shah, D.; Vanza, J.; Misra, A. Lipid based formulation approach for BCS class-II drug: Modafinil in the treatment of ADHD. *J. Drug Deliv. Sci. Technol.,* **2017**, *37*, 166-183. http://dx.doi.org/10.1016/j.jddst.2016.12.012

[178] Cao, Y.; Li, Q.; Liu, L.; Wu, H.; Huang, F.; Wang, C.; Lan, Y.; Zheng, F.; Xing, F.; Zhou, Q.; Li, Q.; Shi, H.; Zhang, B.; Wang, Z.; Wu, X. Modafinil protects hippocampal neurons by suppressing excessive autophagy and apoptosis in mice with sleep deprivation. *Br. J. Pharmacol.,* **2019**, *176*(9), 1282-1297. http://dx.doi.org/10.1111/bph.14626 PMID: 30767208

[179] Cianciulli, A.; Porro, C.; Calvello, R.; Trotta, T.; Lofrumento, D.D.; Panaro, M.A. Microglia mediated neuroinflammation: Focus on PI3K modulation. *Biomolecules,* **2020**, *10*(1), 137. http://dx.doi.org/10.3390/biom10010137 PMID: 31947676

[180] Walker, C.L.; Xu, X-M. PTEN inhibitor bisperoxovanadium protects oligodendrocytes and myelin and prevents neuronal atrophy in adult rats following cervical hemicontusive spinal cord injury. *Neurosci. Lett.,* **2014**, *573*, 64-68. http://dx.doi.org/10.1016/j.neulet.2014.02.039 PMID: 24582904

[181] Gutiérrez-Martín, Y.; Bustillo, D.; Gómez-Villafuertes, R.; Sánchez-Nogueiro, J.; Torregrosa-Hetland, C.; Binz, T.; Gutiérrez, L.M.; Miras-Portugal, M.T.; Artalejo, A.R. P2X7 receptors trigger ATP exocytosis and modify secretory vesicle dynamics in neuroblastoma cells. *J. Biol. Chem.,* **2011**, *286*(13), 11370-11381. http://dx.doi.org/10.1074/jbc.M110.139410 PMID: 21292765

[182] Gómez-Villafuertes, R.; del Puerto, A.; Díaz-Hernández, M.; Bustillo, D.; Díaz-Hernández, J.I.; Huerta, P.G.; Artalejo, A.R.; Garrido, J.J.; Miras-Portugal, M.T. Ca2+/calmodulin-dependent kinase II signalling cascade mediates P2X7 receptor-dependent inhibition of neuritogenesis in neuroblastoma cells. *FEBS J.,* **2009**, *276*(18), 5307-5325. http://dx.doi.org/10.1111/j.1742-4658.2009.07228.x PMID: 19682070

[183] Wu, P-Y.; Lin, Y-C.; Chang, C-L.; Lu, H-T.; Chin, C-H.; Hsu, T-T.; Chu, D.; Sun, S.H. Functional decreases in P2X7 receptors are associated with retinoic acid-induced neuronal differentiation of Neuro-2a neuroblastoma cells. *Cell. Signal.,* **2009**, *21*(6), 881-891. http://dx.doi.org/10.1016/j.cellsig.2009.01.036 PMID: 19385050

[184] Amoroso, F.; Capece, M.; Rotondo, A.; Cangelosi, D.; Ferracin, M.; Franceschini, A.; Raffaghello, L.; Pistoia, V.; Varesio, L.; Adinolfi, E. The P2X7 receptor is a key modulator of the PI3K/GSK3β/VEGF signaling network: evidence in experimental neuroblastoma. *Oncogene,* **2015**, *34*(41), 5240-5251. http://dx.doi.org/10.1038/onc.2014.444 PMID: 25619831

[185] Yu, S.; Hei, Y.; Liu, W. Upregulation of seladin-1 and nestin expression in bone marrow mesenchymal stem cell transplantation via the ERK1/2 and PI3K/Akt signaling pathways in an Alzheimer's disease model. *Oncol. Lett.,* **2018**, *15*(5), 7443-7449. PMID: 29731895

[186] Hu, M.; Li, F.; Wang, W. Vitexin protects dopaminergic neurons in MPTP-induced Parkinson's disease through PI3K/Akt signaling pathway. *Drug Des. Devel. Ther.,* **2018**, *12*, 565-573. http://dx.doi.org/10.2147/DDDT.S156920 PMID: 29588573

[187] Gorbenko, O.; Panayotou, G.; Volkova, D.; Zhyvoloup, O.; Kukharenko, O.; Gout, I.; Filonenko, V. Identification of novel PTEN-binding partners: PTEN interaction with fatty acid binding protein FABP4. *Mol Cell Biochem,* **2010**, *337*(1-2), 299-305. http://dx.doi.org/10.1007/s11010-009-0312-1 PMID: 19911253

[188] Zhao, H.F.; Wang, J.; Shao, W.; Wu, C.P.; Chen, Z.P.; To, S-T.; Li, W.P. Recent advances in the use of PI3K inhibitors for glioblastoma multiforme: current preclinical and clinical development. *Mol. Cancer,* **2017**, *16*(1), 100. http://dx.doi.org/10.1186/s12943-017-0670-3 PMID: 28592260

[189] Waite, K.; Eickholt, B.J. The neurodevelopmental implications of PI3K signaling. *Phosphoinositide 3-kinase in Health and Disease*; Springer, **2010**, pp. 245-265. http://dx.doi.org/10.1007/82_2010_82

[190] Ali, T.; Kim, T.; Rehman, S.U.; Khan, M.S.; Amin, F.U.; Khan, M.; Ikram, M.; Kim, M.O. Natural dietary supplementation of anthocyanins via PI3K/Akt/Nrf2/HO-1 pathways mitigate oxidative stress, neurodegeneration, and memory impairment in a mouse model of Alzheimer's disease. *Mol. Neurobiol.,* **2018**, *55*(7), 6076-6093. http://dx.doi.org/10.1007/s12035-017-0798-6 PMID: 29170981

[191] Chen, Y.L.; Monteith, N.; Law, P-Y.; Loh, H.H. Dynamic association of p300 with the promoter of the G protein-coupled rat delta opioid receptor gene during NGF-induced neuronal differentiation. *Biochem. Biophys. Res. Commun.,* **2010**, *396*(2), 294-298. http://dx.doi.org/10.1016/j.bbrc.2010.04.083 PMID: 20399742

[192] Shojaee, S.; Chan, L.N.; Buchner, M.; Cazzaniga, V.; Cosgun, K.N.; Geng, H.; Qiu, Y.H.; von Minden, M.D.; Ernst, T.; Hochhaus, A.; Cazzaniga, G.; Melnick, A.; Kornblau, S.M.; Graeber, T.G.; Wu, H.; Jumaa, H.; Müschen, M. PTEN opposes negative selection and enables oncogenic transformation of pre-B cells. *Nat. Med.,* **2016**, *22*(4), 379-387. http://dx.doi.org/10.1038/nm.4062 PMID: 26974310

[193] Gaesser, J.M.; Fyffe-Maricich, S.L. Intracellular signaling pathway regulation of myelination and remyelination in the CNS. *Exp. Neurol.,* **2016**, *283*(Pt B), 501-511. http://dx.doi.org/10.1016/j.expneurol.2016.03.008 PMID: 26957369

[194] Mirzaa, G.M. Poduri, A. *Megalencephaly and hemimegalencephaly: breakthroughs in molecular etiology, American Journal of Medical Genetics Part C: Seminars in Medical Genetics*; Wiley Online Library, **2014**, pp. 156-172.

[195] Chen, Y.L.; Law, P-Y.; Loh, H.H. NGF/PI3K signaling-mediated epigenetic regulation of delta opioid receptor gene expression. *Biochem. Biophys. Res. Commun.,* **2008**, *368*(3), 755-760. http://dx.doi.org/10.1016/j.bbrc.2008.01.164 PMID: 18269915

[196] Guan, X-H.; Lu, X-F.; Zhang, H-X.; Wu, J-R.; Yuan, Y.; Bao, Q.; Ling, D-Y.; Cao, J-L. Phosphatidylinositol 3-kinase mediates pain behaviors induced by activation of peripheral ephrinBs/EphBs signaling in mice. *Pharmacol. Biochem. Behav.,* **2010**, *95*(3), 315-324. http://dx.doi.org/10.1016/j.pbb.2010.02.007 PMID: 20170671

[197] Zhang, T.; Shi, Z.; Wang, Y.; Wang, L.; Zhang, B.; Chen, G.; Wan, Q.; Chen, L. Akt3 deletion in mice impairs spatial cognition and hippocampal CA1 long long-term potentiation through downregulation of mTOR. *Acta Physiol. (Oxf.),* **2019**, *225*(1), e13167. http://dx.doi.org/10.1111/apha.13167 PMID: 30053339

[198] Wang, P.; He, Y.; Li, D.; Han, R.; Liu, G.; Kong, D.; Hao, J.; Class, I. Class I PI3K inhibitor ZSTK474 mediates a shift in microglial/macrophage phenotype and inhibits inflammatory response in mice with cerebral ischemia/reperfusion injury. *J. Neuroinflammation,* **2016**, *13*(1), 192. http://dx.doi.org/10.1186/s12974-016-0660-1 PMID: 27549161

[199] Leng, Y.; Wang, Z.; Tsai, L-K.; Leeds, P.; Fessler, E.B.; Wang, J.; Chuang, D-M. FGF-21, a novel metabolic regulator, has a robust neuroprotective role and is markedly elevated in neurons by mood stabilizers. *Mol. Psychiatry,* **2015**, *20*(2), 215-223. http://dx.doi.org/10.1038/mp.2013.192 PMID: 24468826