




Review

# GSK3 $\beta$ Activity in Reward Circuit Functioning and Addiction

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**Abstract:** Glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ), primarily described as a regulator of glycogen metabolism, is a molecular hub linking numerous signaling pathways and regulates many cellular processes like cytoskeletal rearrangement, cell migration, apoptosis, and proliferation. In neurons, the kinase is engaged in molecular events related to the strengthening and weakening of synapses, which is a subcellular manifestation of neuroplasticity. Dysregulation of GSK3 $\beta$  activity has been reported in many neuropsychiatric conditions, like schizophrenia, major depressive disorder, bipolar disorder, and Alzheimer's disease. In this review, we describe the kinase action in reward circuit-related structures in health and disease. The effect of pharmaceuticals used in the treatment of addiction in the context of GSK3 $\beta$  activity is also discussed.

**Keywords:** GSK3 $\beta$ ; reward circuit; addiction; ventral tegmental area; nucleus accumbens



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## 1. Introduction

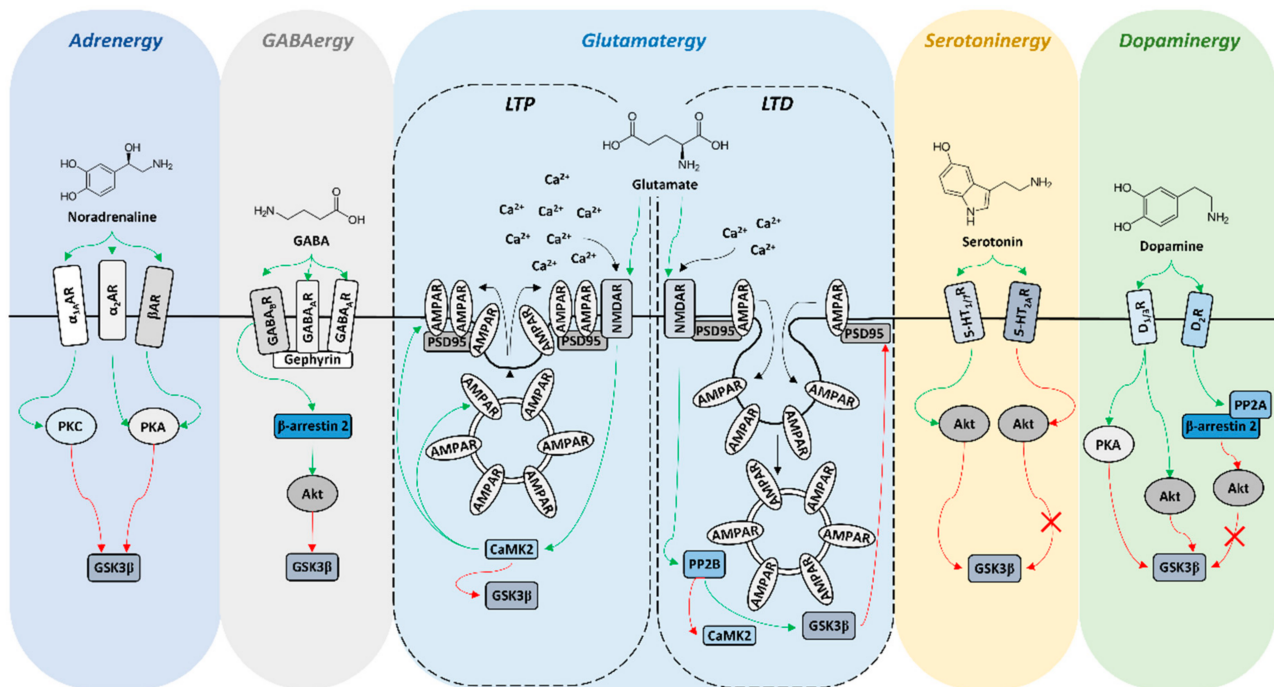
### 1.1. GSK3 $\beta$ Characteristic

Glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ) is a serine/threonine kinase originally described as a negative regulator of glycogen synthase. Its activity is regulated by phosphorylation of residue Tyr216 (taking place during the kinase translation process), which leads to an activation of GSK3 $\beta$  [1], and Ser9, which results in protein inactivation. Residue Ser9 modification is the most important regulatory mechanism occurring on GSK3 $\beta$ . Several kinases and phosphatases are involved in a pSer9-related inhibition of GSK3 $\beta$ , including extracellular signal-regulated kinase (ERK), ribosomal s6 kinase (p90Rsk) [2,3], protein kinase B (Akt) [2,4], cyclic AMP-dependent protein kinase (PKA), mitogen-activated kinases (MAPKs), integrin-linked kinase (ILK), protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A), and protein phosphatase 2B (PP2B also known as calcineurin) [5,6]. The variety of GSK3 $\beta$  upstream regulators makes the kinase activity dependent on many extracellular signals like cytokines, neurotransmitters, neuromodulators, hormones, and growth factors (reviewed in [7]). Additionally, a diversity of the kinase substrates, including glucose metabolism enzymes, transcriptional factors, ion channels, microtubule-associated proteins, synaptic scaffold proteins, and pro- and antiapoptotic factors, positions GSK3 $\beta$  in a center of cell metabolism and makes the kinase a hub connecting different signaling pathways (reviewed in [7]).

GSK3 $\beta$  regulates the development, differentiation, and migration of neuronal precursor cells. There are two variants of the GSK3 $\beta$  gene, named GSK3 $\beta$ 1 and GSK3 $\beta$ 2 [8–11]. These two variants are differentially involved in establishing neuronal polarity and axon guidance [12–15]. They are also involved in the phosphorylation of different substrates [15].

Considering its central role as an integrator of Akt-related pathways [16], GSK3 $\beta$  is involved in dopamine (DA) signaling and responding to addictive drugs, mainly in the *nucleus accumbens* (NAcc) [17]. Downregulation of phosphorylated (activated) Akt leads to a downregulation of phosphorylated (inactivated) GSK3 $\beta$ , thereby increasing the enzymatic

activity of GSK3 $\beta$ . Akt is a negative regulator of GSK3 $\beta$  and its functions are modulated through pathways induced by catecholamines (DA and noradrenaline), serotonin (5-HT),  $\gamma$ -aminobutyric acid (GABA), and glutamate. The scheme of the neurotransmitters actions on GSK3 $\beta$  is presented in Figure 1.



**Figure 1.** Neurotransmitters and neuromodulators influence the activity of GSK3 $\beta$  via their receptors actions. The abbreviations stand for: LTP—long-term potentiation; LTD—long-term depression; AR—adrenergic receptor; PKC—protein kinase C; PKA—protein kinase A; GSK3 $\beta$ —glycogen synthase kinase 3 $\beta$ ; GABA $\beta$ R— $\gamma$ -aminobutyric acid receptor; Akt—protein kinase B; AMPAR -  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR - N-methyl-D-aspartate receptor; PSD95—postsynaptic density 95; CaMK2 - Calcium/calmodulin-dependent protein kinase 2; PP2A—protein phosphatase 2A; PP2B—protein phosphatase 2B; 5-HTR—serotonin receptor; DR—dopamine receptor.

DA induces Akt signaling pathway by stimulation of DA receptor 2 (D<sub>2</sub>R) which results in activation of cAMP-independent signaling [18–20]. The cAMP-independent pathway involves  $\beta$ -arrestin and PP2A which form a complex with Akt and, as a result, decrease Akt activity and increase GSK3 $\beta$  activity [20–22]. However, DA receptor 1 (D<sub>1</sub>R) can also modulate GSK3 $\beta$  activity by the action of Akt. Inhibition of GSK3 $\beta$  decreases the level of plasma membrane-localizing D<sub>1</sub>Rs and its activation in cortical neurons [23].

5-HT receptors also affect GSK3 $\beta$  functions [24]. 5-HT<sub>1/7</sub> receptors (5-HT<sub>1/7</sub>Rs) activation leads to a stimulation of phosphoinositide 3-kinase (PI3K)/Akt signaling pathway. In contrast, activation of 5-HT<sub>2A</sub>R leads to inhibition of the PI3K-Akt pathway, resulting in increased GSK3 $\beta$  activity [24,25].

GABA regulates GSK3 $\beta$  acting through GABA $\beta$  receptors (GABA $\beta$ Rs) which affect  $\beta$ -arrestin 2 activity and thereby stimulate Akt activity, which leads to GSK3 $\beta$  inhibition [26].

GSK3 $\beta$ , when regulated by Akt, modulates the activity of transcription factors such as transcription factor cAMP response element-binding protein (CREB), which action affects learning and memory processes [27–30]. GSK3 $\beta$  regulates also a mammalian target of rapamycin (mTOR) which is essential for memory formation and storage [31,32]. mTOR is involved in the initiation of local translation of synaptic proteins [33,34].

The kinase plays an important role in the regulation of many other transcription factors, like  $\beta$ -catenin, a component of the Wnt signal transduction pathway [35–38]. In addition, GSK3 $\beta$  mediates a signaling pathway exchange into  $\beta$ -catenin-independent Wnt signaling [35]. GSK3 $\beta$  is active in the absence of Wnt [39], and promotes  $\beta$ -catenin

degradation through N-terminal phosphorylation followed by ubiquitination and targeting to proteasomes [40]. In contrast, activation of Wnt receptors leads to an inhibition of GSK3 $\beta$ , which results in a stabilization of  $\beta$ -catenin [41].  $\beta$ -catenin regulates the expression of different types of miRNAs, which play an important role in neuroplasticity [42].

GSK3 $\beta$  activity may also be affected by noradrenaline acting through the  $\alpha_{1A}$ -adrenergic receptor ( $\alpha_{1A}$ AR),  $\alpha_2$ -adrenergic receptor ( $\alpha_2$ AR), and  $\beta$ -adrenergic receptors ( $\beta$ AR).  $\alpha_{1A}$ AR activation effects in residue Ser9 phosphorylation through protein kinase C (PKC) [43], whereas  $\alpha_2$ AR and  $\beta$ AR stimulate residue Ser9 phosphorylation via PKA [44,45].

Glutamate is also involved in the modulation of GSK3 $\beta$  action. N-methyl-D-aspartate receptors (NMDARs), when activated by glutamate, regulate GSK3 $\beta$  activity by its residue Ser9 dephosphorylation [46], which is related to NR2B subunit, and the effect is mediated by the action of PP1 [47]. Importantly, not only NMDARs affect GSK3 $\beta$ , but GSK3 $\beta$  itself regulates the synaptic localization of NR1 and NR2B subunits and thus, NMDAR functions [48,49]. Calcium/calmodulin-dependent protein kinase 2 (CaMK2) and calcineurin [50], which modify residue Ser9, play an important role in the aforementioned processes [51,52]. CaMK2 causes residue Ser9 phosphorylation and thus inhibition of GSK3 $\beta$ , whereas calcineurin dephosphorylates Ser9 and activates GSK3 $\beta$ . Both, CaMK2 and calcineurin, are activated by Ca<sup>2+</sup> presence in the cytoplasm [51,52]. A high concentration of Ca<sup>2+</sup> activates CaMK2, whereas a moderate concentration activates calcineurin [50]. Calcium influx into the cytoplasm is associated with glutamatergic transmission. Glutamate activates  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-Rs), which are responsible for membrane depolarization,  $\neg$  and NMDARs, which are directly involved in calcium current and neuroplasticity. Activation of NMDARs, due to AMPAR-induced membrane depolarization, results in Ca<sup>2+</sup> influx into the cell [53], which leads to an activation of CaMK2 or calcineurin (depending on the Ca<sup>2+</sup> concentration). CaMK2 activity results in the incorporation of AMPARs-containing intracellular vesicles into the postsynaptic membrane, and the synthesis of new AMPAR subunits. The former is considered as the early phase, and the latter as the late phase of long-term potentiation (LTP). GSK3 $\beta$  inhibited by CaMK2 is also involved in the incorporation of AMPARs into the membrane [54]. In contrast, activation of protein phosphatases, including calcineurin, which disinhibits GSK3 $\beta$ , leads to long-term depression (LTD), a process of synapses weakening due to AMPARs internalization. Active GSK3 $\beta$ , which phosphorylates postsynaptic density protein 95 (PSD95) and kinesin light chain 2, regulates the internalization of AMPARs [55].

Given its involvement in the functioning of the reward circuit, GSK3 $\beta$  is considered to be a tempting therapeutic target in addiction treatment [56]. Moreover, the kinase has recently been linked to the pathogenesis and progression of major depressive disorder [57] and schizophrenia [58]. Intensive research is being done on inhibitors of the protein activity, some of which directly affect GSK3 $\beta$ . The inhibitors may be useful in therapies for the aforementioned affective disorders, in which GSK3 $\beta$  is dysregulated [57]. The most significant concern is their selectivity and safety against other kinases, as well as their specific brain distribution in the treatment of central nervous system (CNS) disorders. The categories and further characteristics of particular inhibitors have been described elsewhere (for review see [59]).

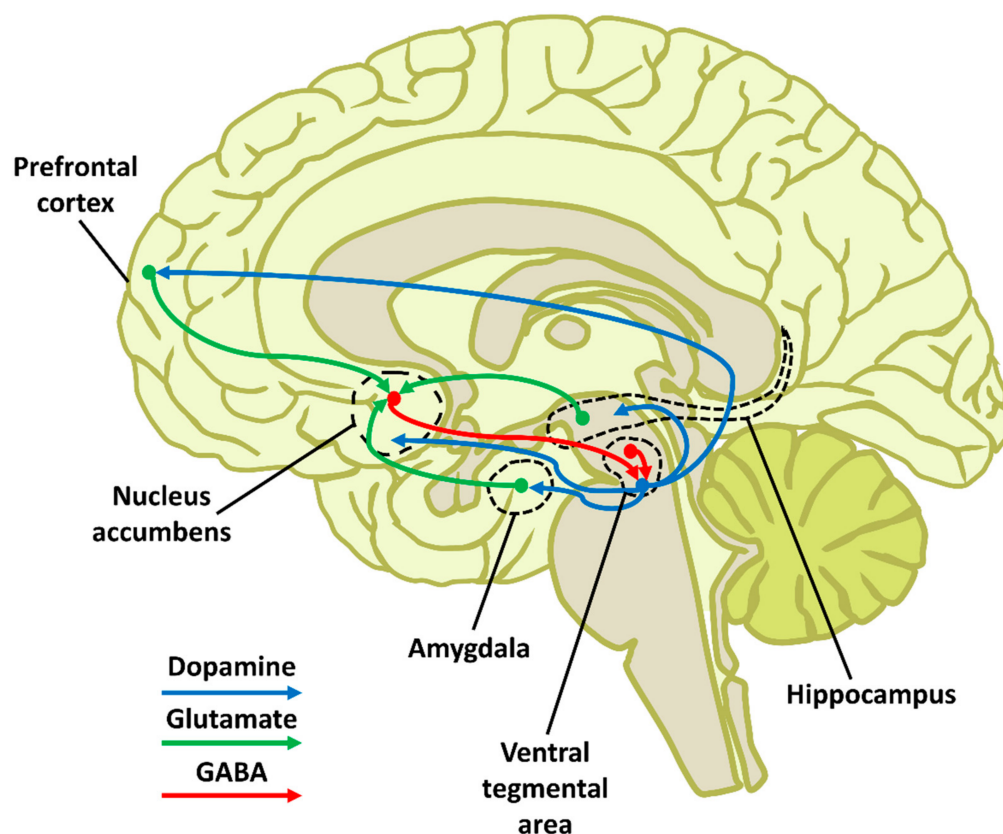
### 1.2. Reward Circuit Anatomy and Functioning

For more than 60 years, tests were made to bring a closer look at the mechanism of the reward circuit. It was discovered by Olds and Milner at McGill University in the early 1950s [60]. Using pharmacological and physiological manipulations, behavioral testing, optogenetic manipulations with brain imaging, and in vivo electrophysiology, scientists got to know the anatomy and pathways of the circuit [61].

The main function of the reward circuit is to promote the individual response to survival-promoting behavior by maximizing contact with beneficial stimuli. The reward system motivates animals to consumer behavior, such as mating, high-calorie food intake,

or social interactions. In that case, the system increases the number of individuals and the likelihood of survival. All these actions induce associative learning, which is characteristic of highly developed species [62]. The impairment of this process, observed in a number of psychiatric conditions, is the clinical symptom of anhedonia.

The system is composed of several brain regions: ventral tegmental area (VTA—a group of dopaminergic neurons on the floor of the mesencephalon), NAcc (mainly GABAergic region in the basal forebrain), prefrontal cortex (PFC), basolateral amygdala (AMY), lateral hippocampus, and medial forebrain bundle [63–66]. All of these components are connected in a triple-synaptic pathway: descending output running from the anterior bed nuclei of the medial forebrain bundle to VTA, an ascending pathway running from VTA to NAcc, and a further ascending projection running from NAcc to the ventral pallidum [67,68]. The first pathway is probably associated with glutamate neurotransmission [69], the second with DA, and the third uses GABA, substance P, and enkephalin as neuromodulators [70–72]. All of these neuronal projections create a coherent relationship between processing emotions, connecting them with the situation, and triggering the appropriate response. Moreover, all the processes are also connected to the hippocampus and allow the subject to remember the pleasurable situation. The simplified scheme of the anatomy of the reward circuit is illustrated in Figure 2.



**Figure 2.** The schematic illustration of the anatomy of the human reward circuit. The main structures of the circuit are delineated with dash lines and the main projections are presented in colors.

The basal ganglia are a central area for monitoring and developing motivated behaviors [73]. NAcc, which is a part of the basal ganglia area, is the main data manager of the reward circuit. It is involved in the cognitive processing of rewards and determining the desirability of stimuli as well as acquiring and eliciting conditioned behaviors that facilitate future reward-seeking behavior. VTA consists of the GABAergic and dopaminergic neurons releasing DA into the forebrain, ventral striatum, and PFC via the mesolimbic pathway. VTA responds to glutamate when reward stimuli are present. When PFC receives

the signal from VTA, it starts to process the information and helps to focus on a pleasant action. The anterior cingulate and orbitofrontal gyri are areas that determine the salience of stimuli and the reaction, and send information to NAcc to control impulsive reactions for stimulus. Current evidence suggests that VTA modulates the stimulus by different subtypes of dopaminergic neurons. VTA projects excitatory input to NAcc, and aversive to the PFC in response to cocaine stimulus [74,75]. The rewarding effect in NAcc depends on the rate of DA release. DA binds to the low-affinity D<sub>1</sub>R and gives a drug reward, or to the high-affinity D<sub>2</sub>R, which does not give a drug reward. However, the strongest effect is exerted when both the D<sub>1</sub> and D<sub>2</sub> receptors are activated [76]. Hippocampus is responsible for connecting situations-specific memories of people, places, and things with pleasure and remembering them. Efferent hippocampal cells partially depolarize NAcc, making it more easily excitable. Basolateral AMY is a center of input and processing of emotions, also responsible for conditioned learning and integration between environmental signaling and memory of previous reward or aversion. Together with the hippocampus, AMY translates the emotion into specific outcomes [77]. The dorsal raphe nucleus is a center of serotonergic neurons and regulates mood and modulates the reward pathway [77].

### 1.3. Addiction Mechanism

Neuroscience describes addiction as a chronic brain disease, which has strong genetic, cultural, and neurodevelopmental connections. In the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5), addiction occurs as a description of the clinical observation of the patient's symptoms, which can include cognitive, emotional, and physical symptoms, such as impaired control (more of the substance is used, the substance is used more often, and the patient wants to stop using the substance but is not able to), social problems (inability to complete tasks, giving up activities the patient used to care about because of the substance use, and neglecting responsibilities), risky use (continued use despite known problems), and physical dependence (needing more of the substance to get the same effect, and having withdrawal symptoms when the substance is not used) [78]. It is important to pay attention to the difference between addiction and physical dependence. Physical dependence is the result of developing tolerance to the drug. Addiction is a disease characterized by the steadily progressive use of the drug that leads to harm to the addicted one. Contrastingly, drugs like cocaine cause strong addiction, but not physical dependence. Furthermore, laboratory animals self-administered the addictive drug despite the lack of physical dependence, intolerance, or withdrawal [79]. Ethanol, barbiturates, and opiates produce physical dependence [80–82].

Activation of the reward system by chemical substances results in neuroplastic changes and dysregulation in the motivational system, which could be demonstrated with mice receiving their favorite food containing a toxic substance or an addictive drug together with the toxin. After eating poisoned food, mice were not willing to eat this food again, differently when food contain the addictive drug, despite adverse effects.

Two molecular mechanisms leading to persistent addiction are suspected: long-lived or permanent up- or down-regulation (sensitization or tolerance) of the expression of crucial molecular pathways, or a brief burst of gene expression or protein translation that confers long-term alterations on behavior by causing the physical remodeling of synapses and circuits [83].

Different drugs affect different neurotransmitters and initiate various reactions. All abusive drugs, like cocaine, amphetamine, opiates, nicotine,  $\delta^9$ -tetrahydrocannabinol (THC), and alcohol enhance the secretion of DA in the brain reward system. Cocaine and amphetamine exert their action in NAcc and AMY. Opiates affect mainly opioid receptors (OR), nicotine influences nicotinic cholinergic receptors (nAChRs) and GABA receptors, THC and alcohol affect endocannabinoid receptors (CB) and OR. All the drugs activate the reward circuit by dopaminergic effect and induce a period of decreased DA activity during withdrawal which leads to neuroadaptation [84].

NAcc is composed mainly of GABAergic medium spiny neurons (MSNs) and receives DA and glutamine inputs. However, the cells can be divided into two families: D1-type family (containing D<sub>1</sub>-like DA receptors and dynorphin) and D2-type family (containing D<sub>2</sub>-like DA receptors and enkephalin) [85]. In response to drug exposure, D1-type induces sensitization and increases the rewarding effects of a drug of abuse. In contrast, D2-type desensitizes the rewarding effect [86]. Chronic substance abuse leads to a decrease in DA receptor density and reward metabolism. This downregulation results in a diminished ability of low-activity stimuli to activate the sensitivity of the reward system. Long-term suppression of the reward system leads to the deterioration of the drug abuser's mental state. The lack of satisfaction from performing potentially pleasurable activities leads to repeated administration of an addictive drug because it is the easiest and possible way to feel pleasure and activate the reward system [87,88].

Studies by Shultz et al. have shown that not only direct contact with a drug stimulates dopaminergic neurons, but also learned signals that precede the administration of the drug. When a stimulus is presented in the environment that normally precedes drug administration, dopaminergic neurons are activated, but if the drug is not delivered, the system is silenced. If the drug is administered, reinforcement occurs, which shows the link between the whole reward system mechanism and associative learning [89,90]. It is suspected that the stimulus-response may be related to Pavlovian-to-Instrumental-Transfer (PIT). Pavlovian effects may directly influence behavior and have a strong impact on drug relapse [91,92].

DA not only transmits signals to the entire system but also activates several molecular pathways. It binds to the D<sub>1</sub>Rs, which activates CREB that leads to increased transcription of  $\Delta$ FosB [93,94]. Fos family proteins, which include c-Fos, FosB, Fra1, and Fra2, heterodimerize with Jun proteins (c-Jun, JunB, JunD) to construct active transcription factor complex—AP1 [95,96].  $\Delta$ FosB naturally accumulates in NAcc [95] in response to drug or natural reward, such as consumption of sucrose or high-fat food, as well as physical activity. Its expression is selectively dependent on substance P in the dynorphin subset of MSN [97,98]. Studies conducted on transgenic mice with overexpression of  $\Delta$ FosB have shown a greater increase in locomotor response (50% higher than wild-type mice) to cocaine exposure. The higher activity remained constant throughout the period of chronic cocaine administration. Studies showed that selective induction of FosB in dynorphin neurons is involved in the enhanced stimulus-response, which may suggest that in humans, overexpression induced by exposure to cocaine may also lead to long-term enhanced sensitivity to the stimulus and reward effects of the drug, which may indirectly affect the development of a state of addiction [96,99]. It is suggested that the main targets for the transcription factor are: AMPAR subunit GluR2 and gene encoding dynorphin. Overexpression of GluR2 in the NAcc, by the use of virus-mediated gene transfer, increased the sensitivity of animals to the rewarding effects of cocaine, thereby mimicking partially the phenotype observed in  $\Delta$ FosB-overexpressing mice [96]. GluR2 expression induction may explain the reduced electrophysiological sensitivity of NAcc neurons to AMPAR agonists after chronic cocaine administration because GluR2-containing AMPAR exhibit reduced overall conductance and reduced Ca<sup>2+</sup> permeability. The reduced response of these neurons to excitatory stimuli may enhance responses to the drug of abuse [100]. Another target for  $\Delta$ FosB is dynorphin, the opioid peptide which is an endogenous ligand for the  $\kappa$ -opioid receptor ( $\kappa$ OR). The dynorphin/ $\kappa$ OR system modulates the activity of dopaminergic and glutamatergic neurons. Dynorphin inhibits dopaminergic neurons innervating MSN because of  $\kappa$ OR presence on dopaminergic nerve terminals in the NAcc and also on the perikaryons and dendrites in VTA. However, dynorphin expression is differentially regulated by CREB and  $\Delta$ FosB. The former induces dynorphin expression in NAcc and reduces the rewarding properties of the drug of abuse, and the latter decreases the opioid peptide expression, which contributes to the enhancement of the reward mechanism seen with  $\Delta$ FosB induction. Because drug-induced CREB activation dissipates rapidly after the administration of the drug, the

reciprocal regulation of dynorphin by CREB and  $\Delta$ FosB explains the reciprocal changes in behavior that occurs during the early and late phases of withdrawal [94,101–103].

DA and glutamate levels in NAcc are reduced during the early phase of drug abstinence. However, gene expression and protein translation are still observed. Molecular changes and decreased DA activity during withdrawal lead to compulsive drug-seeking and increase dosing.

Studies on human species: family, adoption, and twins, demonstrated the genetic basis in susceptibility to addiction [104,105]. Both genetic and environmental factors create the behavioral phenotype of addiction. Moreover, environmental and social factors can also influence the neurobiological substrates of addiction [106]. However, there is no single gene responsible for addiction. The genetic factors related to the secretion of neurotransmitters which affects personality and temperament. Studies on healthy adult men showed that those with high levels of DA in the striatum find the psychostimulant methylphenidate unpleasant, while men with striatal DA deficiencies find methylphenidate pleasant. The research shows that, in line with Blum's assumptions, reward deficiency can be a factor of addiction [107–109].

## 2. GSK3 $\beta$ Expression Profile in the Reward Circuit-Related Structures

Regarding the reward system, GSK3 $\beta$  is known to be highly expressed in the hippocampus, NAcc, PFC, and AMY [110]. However, its expression is suppressed in most pyramidal neurons in the cortex and in about 50% of neurons in the *Cornu Ammonis* 1 region (CA1) of the hippocampus [111]. Furthermore, it was shown that there is a nearly 50% reduction in GSK3 $\beta$  mRNA in the human brain in adults compared to adolescents [112].

The altered expression of GSK3 $\beta$  is often associated with various diseases as well as addiction-related behaviors. It has been demonstrated that rats with knockdown of GSK3 $\beta$  in NAcc suffered from increased depression and addiction behaviors. It can be concluded that GSK3 $\beta$  has modulatory effects at different levels of stress exposure [113]. Reduced GSK3 $\beta$  expression in the PFC was discovered in suicidal adolescents [112]. Overexpression of GSK3 $\beta$  may also contribute to neurodegenerative diseases [114,115].

## 3. GSK3 $\beta$ Activity in the Reward Circuit

Considering that GSK3 $\beta$  is highly expressed in many structures of the reward system, the activity of the kinase should play an important role in the functioning of the system and significantly affects occurring processes.

One of the most important structures in the reward system is NAcc, in which activation of Akt leads to phosphorylation of the transcription factor CREB, which activates the expression of genes involved in neuronal plasticity [27–30]. Inhibition of GSK3 $\beta$  through the Akt signaling pathway in NAcc leads also to activation of mTOR, which initiates the induction of mRNA-dependent translation of the microtubule-binding protein CRMP-2 important in learning and memory formation [116–118]. GSK3 $\beta$  activity in the NAcc influences the development of preference for the place and is involved in object localization tasks [119]. Activation of GSK3 $\beta$  in NAcc is associated with the development of social failure in susceptible mice. This is supported by the fact that when the dominant-negative form of the kinase is expressed in NAcc, mice are resistant to social failure. This indicates that GSK3 $\beta$  activity in NAcc may play an important role in mediating resistance to social stress [111].

Increased GSK3 $\beta$  activity in the NAcc core (NAccC) is associated with increased locomotor activity, whereas inhibition of the kinase in the NAccC attenuates behavioral sensitization and decreases locomotor activity [120]. GSK3 $\beta$  activity in NAccC is important in the induction of psychostimulant-induced sensitization, however, the molecular mechanism remains unclear [120].

GSK3 $\beta$  activity in NAcc shell (NAccSh) influences behaviors associated with addiction, depression, and anxiety. Studies in rats showed that knockdown of GSK3 $\beta$  reduces neuronal activity in tonically autoactive neurons (TAN) in the NAccSh. TANs play impor-

tant roles in behaviors associated with addiction, depression, and anxiety. However, the exact mechanisms by which GSK3 $\beta$  causes changes in NAccSh have not been elucidated and require further studies [121].

GSK3 $\beta$  shows significant activity in the hippocampus, where it mediates glutamate receptor activity and synaptic plasticity [122–124]. Interactions between GSK3 $\beta$  and NMDAR in the hippocampus provide evidence for a link between GSK3 $\beta$  and LTP/LTD [47,125,126]. Studies in the rat hippocampus showed that activation of GSK3 $\beta$  inhibits LTP [124], whereas inhibition of GSK3 $\beta$  activity inhibits LTD. Thus, activation of GSK3 $\beta$  is necessary to induce LTD, while decreased GSK3 $\beta$  activity is necessary to induce LTP [127]. LTP inhibition in the hippocampus by GSK3 $\beta$  activity impairs learning, memory recall, and reconsolidation [128,129]. The over-activity of the kinase in the hippocampus is detrimental because it is associated with inflammatory processes and oxidative damage, which hinders the formation of new neuronal connections. This results in reduced plasticity and dendritic spines density. Impaired social interaction is also observed when the kinase is overexpressed [130].

Inhibition of Akt by DA in the mouse striatum appears to contribute to two types of D2-like DA receptors, D<sub>2</sub>R and D<sub>3</sub>R, while D<sub>1</sub>R and D<sub>4</sub>R are not involved in the signaling [21,131–134]. Transient stimulation of D<sub>2</sub>R leads to an increased level of Akt phosphorylation, which is followed by phosphorylation of GSK3 $\beta$  [131,135], whereas prolonged D<sub>2</sub>R stimulation causes reduced Akt phosphorylation and increases GSK3 $\beta$  activity in the dorsal striatum [132,136].

GSK3 $\beta$  has been shown to be involved in the diurnal variation in the expression of the conditional place preference, but not in the acquisition of the cocaine-induced conditional place preference in VTA. However, the precise mechanisms that mediate these processes are not known [137].

GSK3 $\beta$  activity is also linked to the medial PFC (mPFC). Knockout of GSK3 $\beta$  in D<sub>2</sub>R mPFC neurons causes an anxiety-like behavior, impairs working memory and social interactions. In addition, the kinase knockout in mPFC neurons has a significant impact on neuronal transcriptomes and significantly affects pathways related to synaptic function. Accordingly, GSK3 $\beta$  activity in adult D<sub>2</sub>R mPFC neurons contributes to behavioral regulation, affecting cognitive function, social interactions, and protects against anxiety-like behaviors [138].

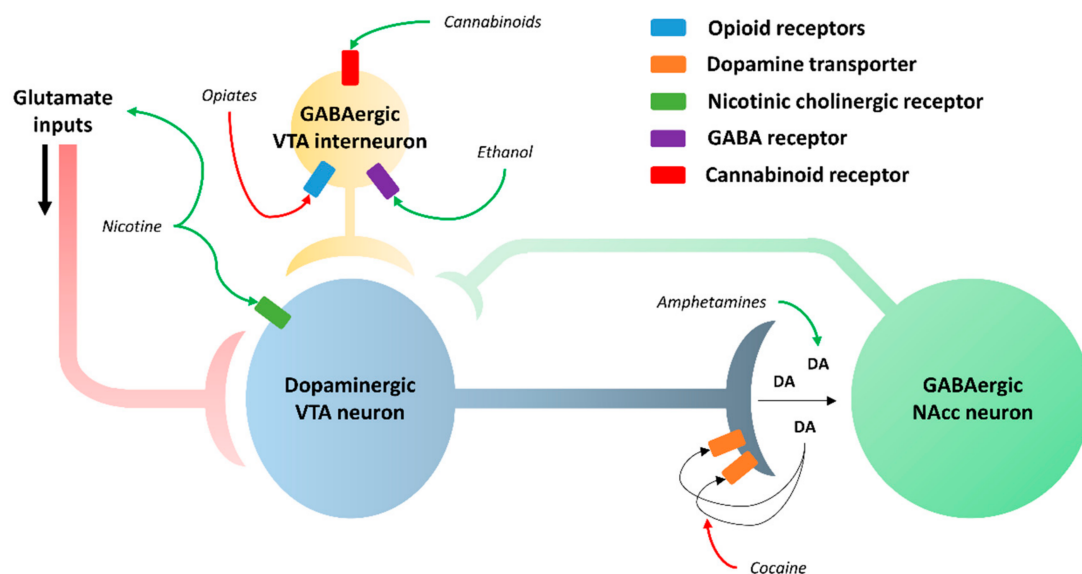
GSK3 $\beta$  activity in AMY significantly affects decision-making related to the assessment of benefits and losses. However, molecular mechanism is still unknown and further researches are needed [139].

In conclusion, the activity of GSK3 $\beta$  is modified by many different signaling pathways in the reward circuit. The kinase activity is different depending on the structure it affects. Active GSK3 $\beta$  weakens synapses and decreases neuronal excitability, while GSK3 $\beta$  inhibition is essential for the induction of LTP, a major mechanism involved in learning and memory formation. Addiction is a disorder that pathologically regulates the underlying mechanisms of learning and memory [140–147] suggesting a key role for GSK3 $\beta$  which significantly affects these processes.

#### 4. Role of GSK3 $\beta$ in Addiction

The mechanism of addiction is related to a dysregulated neurotransmission, which can induct signaling pathways that regulate GSK3 $\beta$  functions. Addictive substances lead to increased levels of extracellular DA, 5-HT, glutamate, and noradrenaline in the reward system. Depending on the type of neurotransmitter, different receptors are responsible for signal transduction (Figure 3) [118,148–151].





**Figure 3.** Simplified scheme of converging acute actions of drugs of abuse on the VTA-NAcc. The abbreviations stand for: VTA—ventral tegmental area; NAcc—nucleus accumbens; DA—dopamine.

Many studies on the effects of psychostimulants on GSK3 $\beta$  activity in the reward system have been made. There are no reports on the effects of these substances on GSK3 $\beta$  expression in relation to the reward circuit during postnatal life. It is only known that cocaine-treated rabbits in utero had no changes in GSK3 $\beta$  expression in the brain at day 20 of postnatal life [152]. It appears that the regulation of the kinase activity is highly dependent on the time after administration of a given stimulant. Changes in the level of Akt and GSK3 $\beta$  phosphorylation in the brain were detected 15–120 min after administration of psychostimulants, e.g., cocaine or amphetamine. A rapid increase in the phosphorylation of GSK3 $\beta$  [153,154] and Akt [155] in the striatum was identified 15–20 after the administration of the drug. 30–120 min after psychostimulant administration, GSK3 $\beta$  is activated by its dephosphorylation. It has been documented that a significant decrease in residue Ser9 phosphorylation of GSK3 $\beta$  and residue Thr308 phosphorylation of Akt occurs 30 min after cocaine administration [156,157] and 90–120 min after amphetamine administration [131,155]. It appears that after a short time of amphetamine administration Akt is regulated by D<sub>1</sub>R and after about an hour D<sub>2</sub>R becomes involved [158].

Increased GSK3 $\beta$  activity is also affected by prolonged exposure to psychostimulants. In NAcc [120,159,160] and in VTA [161], reduced GSK3 $\beta$  phosphorylation was observed after cocaine and amphetamine administration. Furthermore, regular cocaine administration is found to increase GSK3 $\beta$  phosphorylation in the frontal cortex [162], but acute cocaine does not cause any changes in this brain area [157].

GSK3 $\beta$  is a key factor in addiction development. NAcc is essential in the mechanism of cocaine addiction [157,163] since the kinase activity in NAcc has been shown to increase after exposure to cocaine [156,163]. Thus, it can be concluded that GSK3 $\beta$  activation is essential for the rewarding effects of cocaine.

There is a positive correlation between the level of GSK3 $\beta$  and cocaine preference scores [119]. Knockdown of GSK3 $\beta$  in mice resulted in reduced ability to develop a cocaine-induced place preference [157] and in turn, low levels of GSK3 $\beta$  in NAcc resulted in a lack of preference for cocaine-paired environments [119]. Interestingly, administration of cocaine to rats for 14 days resulted in a decrease of GSK3 $\beta$  phosphorylation on residue Ser9 in the NAcc, despite that it was not observed in NAccSh [120]. Similar observations were made for amphetamine derivatives. The administration of methamphetamine (METH) resulted in an increase in the level of residue Ser9 phosphorylated GSK3 $\beta$  in the NAcc, but in NAccSh it was not observed [159,164], which means that increased exposure to METH led to increased activity of GSK3 $\beta$  in the NAcc [165]. In addition, METH significantly

increases GSK3 $\beta$  residue Ser9 phosphorylation and pSer9 GSK3 $\beta$ /Ser9 GSK3 $\beta$  expression in PFC, hippocampus, and VTA. On the contrary, cannabidiol (CBD) treatment for 1 h prior to METH administration decreased the level of pSer9 GSK3 $\beta$  and pSer9 GSK3 $\beta$ /Ser9 GSK3 $\beta$  expression levels in the four structures related to the reward circuit mentioned above in a dose-dependent manner compared to the group in which METH alone was administered. Therefore, it can be concluded that CBD can suppress METH-induced pSer9 GSK3 $\beta$  protein expression in PFC, NAcc, hippocampus, and VTA [160].

Psychomotor stimulants, such as cocaine or amphetamine, are known to activate dopaminergic neurotransmission in NAcc, which results in increased locomotor activity [166,167]. It is also well known that DA participates in a pathway mediated by cAMP. However, it turns out that DA also has a signaling pathway involving GSK3 $\beta$ . The use of GSK3 $\beta$  inhibitors that cause an increase in the phosphorylation level at Ser9, and thus, presumably a decrease in the kinase activity, has been shown to alleviate hyperactivity induced by the administration of psychomotor drugs such as cocaine or amphetamine [156,168]. Interestingly, microinjection of the inhibitor SB216763 into the NAcc results in a blockade of expression of locomotor sensitization induced by multiple injections of these psychomotor stimulants [120,165]. Another study showed that inhibition of temporal GSK3 $\beta$  inactivation in NAcc by downregulating Ser9 phosphorylation enhances the hyper-locomotor activity caused by cocaine administration [169]. Therefore, it could be concluded that drug-induced locomotor activity is dependent on GSK3 $\beta$  activity in the NAcc.

The effect of cocaine on Akt activity is observed in NAcc and AMY but has no association with the hippocampus [163]. Importantly, these effects depend on the time of cocaine administration. In NAcc a decrease in Akt activity is observed after 1 day. In AMY, the activity of Akt is higher after 1 day, remains unchanged after 3 days of daily administration of cocaine, and after 14 days of daily administration GSK3 $\beta$  activity is decreased. After 14 days of daily cocaine administration, the level of phosphorylated GSK3 $\beta$  was notably reduced, which may suggest that in AMY GSK3 $\beta$  is not the only substrate of Akt after cocaine administration [163].

Cocaine-induced changes in GSK3 $\beta$  activity can also cause changes in NAccSh functioning. Studies in rats have shown that the knockdown of GSK3 $\beta$  in the NAccSh resulted in an increased activity associated with self-administration of cocaine, which occurs particularly at high doses of cocaine [121].

GSK3 $\beta$  signaling is also required in the reconsolidation of memories linked to cocaine reward [170]. Some upstream factors control GSK3 $\beta$  activity that is necessary for cocaine reward memory, such as subtypes of NMDAR subunits: GluN2A and GluN2B [171–175]. Those receptor subunits are activated during the memory reactivation and stimulation of these subunits-containing receptors activate GSK3 $\beta$  by dephosphorylation at Ser9 [47,175]. GluN2A receptors are blocked before the recollection of cocaine reward memory, which blocks GluN2B dephosphorylation in NAcc. Based on this information, GluN2A receptors participate in the GSK3 $\beta$  activation after cocaine reward recall. It is also known that GluN2B receptors have a very similar role [175]. Cocaine administration to rats upregulates GSK3 $\beta$  through stimulation of DA receptors [176].

It was shown that mice with GSK3 $\beta$  knockout have reduced activity after amphetamine injection compared to wild-type mice [131], while transgenic mice overexpressing GSK3 $\beta$  showed increased locomotor activity [177].

In contrast to psychostimulants, administration of opioids is not correlated with higher activity of GSK3 $\beta$  in NAcc [178]. Knockdown of GSK3 $\beta$  in NAcc impairs the development of site preference when cocaine is used, whereas no such effect is observed with morphine treatment [179]. When GSK3 $\beta$  levels were reduced, the mice showed a preference for a morphine-paired environment [119]. Furthermore, it was found that when rats were in the morphine-paired zone, MSNs in the NAcc showed their firing frequency during morphine-induced site preference expression [178]. It could be concluded that the activation of GSK3 $\beta$  is involved in the cocaine reward process, but is not necessary for morphine reward [119]. It is shown that there is an increase in pSer9 GSK3 $\beta$  level

when morphine is administrated. This is supported by the fact that for the morphine withdrawal group, GSK3 $\beta$  phosphorylation decreases, compared to the morphine intake group. Treatment of animals with morphine results in decision-making problems, which are associated with increased levels of pSer9 GSK3 $\beta$  [138].

In mice, ethanol administration leads to activation of PI3K and Akt, which causes GSK3 $\beta$  phosphorylation at Ser9 in NAcc [180,181]. That inhibits GSK3 $\beta$  activity, which in turn activates the transcription factor CREB [182]. Exposure to ethanol during fetal development also changes GSK3 $\beta$  activity in the fetal brain [183,184]. The Wnt signaling pathway, in which GSK3 $\beta$  is involved, is extremely important for proper axis formation during embryonic development [56].

It is well known that the PFC is involved in mediating reward-seeking-related behaviors [185,186], as well as negative emotional states [187]. mPFC is also known to play an important role when it comes to withdrawal and alcohol-seeking behaviors [188]. Studies have shown that reduced mPFC activity associated with its dysregulation is associated with anxiety disorders [189,190], and that mPFC activation is altered in healthy individuals who have been exposed to anxiety stimuli [191]. Thus, it can be speculated that molecular mechanisms which are dysregulated in mPFC may be involved in alcohol withdrawal anxiety.

Studies in rats have shown that GSK3 $\beta$  activity in mPFC may be associated with the negative effects of ethanol withdrawal. GSK3 $\beta$  inhibition provides protection against ethanol neurotoxicity, whereas increased GSK3 $\beta$  activity results in sensitization of neurons to the toxic effects of ethanol. As ethanol neurotoxicity may contribute to cognitive decline, it is possible that a reduction of cells loss through GSK3 $\beta$  inhibition may prevent binge drinking and relapse [192]. GSK3 $\beta$  affects mPFC functions associated with ethanol seeking via brain-derived neurotrophic factor (BDNF). Overexpression of GSK3 $\beta$  leads to reduced levels of BDNF protein in mPFC. BDNF is transported from the mPFC to the ventral and dorsal striatum. The factor levels in the striatum increase after alcohol consumption, leading to alcohol aversion. Accordingly, GSK3 $\beta$  is inhibited after alcohol consumption, resulting in reduced BDNF secretion, so the amount of BDNF in the striatum is reduced, leading to a relapse of ethanol seeking [193]. A positive correlation was found between ethanol intake and GSK3 $\beta$  expression. Ethanol consumption leads to GSK3 $\beta$  overexpression, which makes the brain more sensitive to the anxiety effects of ethanol abstinence, resulting in increased ethanol self-administration [194]. It is known that during repeated cycles of excessive alcohol administration and withdrawal, the activity of Akt and PI3K signaling in the NAcc is increased [181], and phosphorylation at Ser9 residue of GSK3 $\beta$  is increased [195]. Activation of these signaling pathways also occurs in mPFC during ethanol withdrawal, resulting in activation of the transcription factor CREB [182]. Therefore, it is possible that the PI3K-Akt-GSK3 $\beta$ -CREB pathway in mPFC is involved in anxiety behaviors associated with alcohol withdrawal.

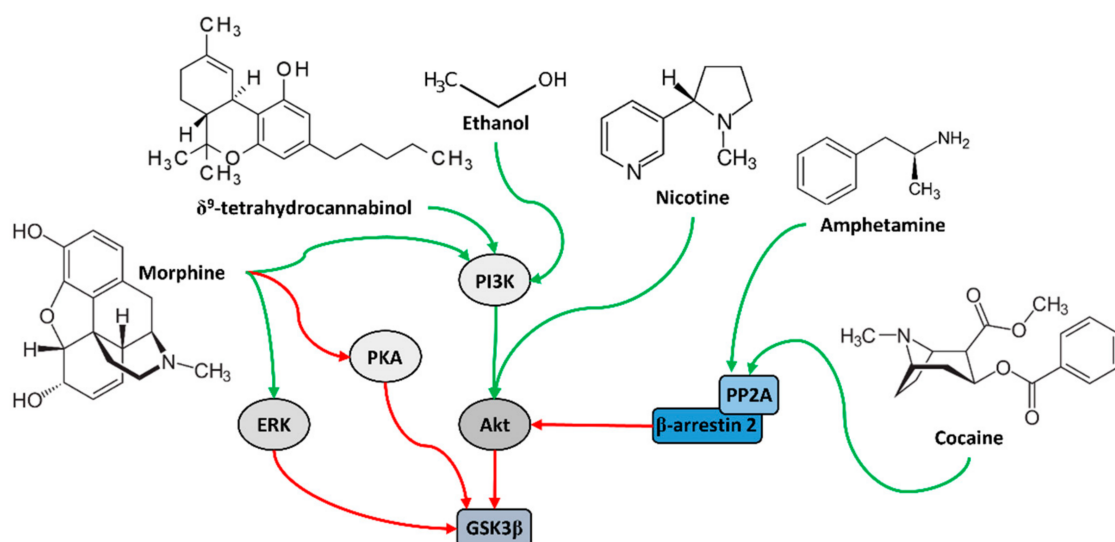
Excessive alcohol consumption initiates the translation of several mTOR-dependent mRNAs in rat NAcc. Importantly, all of these proteins contribute to synaptic functions. By inducing the translation of synaptic proteins, mTOR enables neuroadaptations resulting from excessive alcohol intake. Induction of mTOR activity is enabled by inhibition of GSK3 $\beta$ , confirming its important role in ethanol dependence [194].

It is unclear whether nicotine exposure plays a direct role in Akt-GSK3 $\beta$  signaling in single neurons. However, *in vitro* studies have shown that nicotine is an activator of the Akt-GSK3 $\beta$  pathway in lung cancer cells [196]. Adolescent rats also showed a selective increase in phosphorylation of GSK3 $\beta$  after nicotine administration [197].

Cannabinoids are said to have neuroprotective functions [198–203]. Some of these neuroprotective functions are associated with the activation of the PI3K/Akt pathway. Cannabinoids appear to be capable of activating this pathway [204–206] by acting on the CB1 and CB2 receptors [207]. THC activates PI3K/Akt pathway via stimulation of CB1, leading to phosphorylation and inactivation of GSK3 $\beta$  in the mouse brain. The effects of THC on Akt and GSK3 $\beta$  were dose-dependent and not dependent on MAPK activation in

the hippocampus [208]. In the striatum, activation of the Akt/GSK3 $\beta$  pathway by THC was not dependent on dopaminergic transmission [209,210]. The pool of phosphorylated Akt was associated with the cell membrane, whereas the cytosolic pool showed no major level of phosphorylation. On the contrary, GSK3 $\beta$  phosphorylation level after THC administration was increased for both the membrane and cytosolic pools, which indicates that inactivation of GSK3 $\beta$  by THC is independent of its subcellular localization. GSK3 $\beta$  activity was shown to be tightly regulated by CB1, as its blockade by the inhibitor rimonabat also decreased the kinase phosphorylation level. Application of wortmannin, which is an irreversible PI3K inhibitor, abolished Akt phosphorylation, whereas GSK3 $\beta$  phosphorylation was only slightly reduced, indicating the presence of other pathways involved in the regulation of GSK3 $\beta$  upon THC administration. However, it has not been shown which pathways might be involved, thus further research is needed [208].

Under the influence of addictive substances, both the expression and activity of GSK3 $\beta$  are altered through a number of signaling pathways that are highly important in the functioning of the CNS. Drug-regulated GSK3 $\beta$  activity and function vary depending on the structure of the reward system it affects. Consequently, targeting GSK3 $\beta$  may be helpful in treating addiction induced by substances that significantly affect the kinase. Summarizing illustration of the effects of particular drugs of abuse on the kinase activity is presented in Figure 4.



**Figure 4.** Drugs of abuse affect the activity of GSK3 $\beta$  via the kinase upstream regulators. The abbreviations stand for: ERK—extracellular signal-regulated kinase; PI3K—phosphoinositide 3-kinase; PKA—protein kinase A; Akt—protein kinase B; GSK3 $\beta$ —glycogen synthase kinase 3 $\beta$ ; PP2A—protein phosphatase 2A.

### 5. Addiction Treatment and Its Effect on GSK3 $\beta$

GSK3 $\beta$  is widely known to be a target of pharmaceuticals used in addiction treatment. Memories of drug exposure in NAcc are highly resistant to extinction. The reward circuit, when activated, is involved in the reconsolidation of previously learned memories. The disruption of reward memories may potentially be the treatment in drug addiction [170]. Inhibition of the kinase during memory retrieval may obliterate the place preference of the cocaine. It also attenuates hyperactivity and prevents the development of sensitization of the drugs following their repeated administration [168]. Multiple studies in mice show that selective inhibition of GSK3 $\beta$  by SB216763 reduces the development and expression of behavior induced by amphetamine or cocaine [168,170]. Knockdown of GSK3 $\beta$  allowed to analyze the role of the protein in NAccSh in addiction-related behaviors. The results implicate that inactivation of GSK3 $\beta$  increases cocaine-taking and seeking behavior. It may also influence DA signals [121].

PFC is involved in alcohol-seeking behavior and withdrawal. Alcohol-mediated activation of PI3K and Akt results in inhibition of GSK3 $\beta$  and activation of CREB. Wortmannin, the PI3K-Akt-GSK3 $\beta$ -CREB signaling pathway inhibitor, is a potential candidate to be used in alcohol abuse treatment. Intra-mPFC injection of wortmannin in rats caused an inhibition of PI3K and reversed the behavioral effects of withdrawal [182]. The inhibitor reduced alcohol intake and, by disturbing GSK3 $\beta$ , decreased anxiety-related behavior in alcohol-exposed rodents [211]. However, wortmannin is not a specific GSK3 $\beta$  agonist, and it has not yet been tested, whether enhancing the phosphorylation of PI3K-Akt-GSK3 $\beta$ -CREB pathway increases the anxiety-like behavior caused by alcohol abuse.

Bupropion is seemed to be a tempting target of the research on addiction treatment. It is a drug used in the treatment of METH addiction. It works by inhibiting the reuptake of monoamine through DA transporters (DAT). As a result, there is an increase in striatal extracellular DA levels in rats. However, the precise pharmacological mechanisms of action are unclear and the efficiency has not been confirmed in the human striatum. The main consequence of addiction treatment is its effect on the pharmacological inhibition of GSK3 $\beta$  (Table 1), which significantly limits DA-dependent locomotor behaviors [131]. However, it is important to remember that inhibition of GSK3 $\beta$  does not completely suppress DA-mediated behavior. DA functions are controlled by a complicated signaling network and full response depends on the cooperation of all components of the pathway.

Naltrexone and acamprosate are two medications shown to be efficacious for relapse prevention in alcohol addiction treatment. Acamprosate is a putative glutamate receptors antagonist, while naltrexone is an opioid-antagonist [212]. The comparison of efficacy profiles shows that each drug gives different effects on certain drinking outcomes. Naltrexone blocks endogenous opioids triggered by alcohol and consequently decreases dopaminergic activity. Therefore, it reduces heavy drinking and craving, by decreasing the positive reinforcing effects of alcohol if drinking occurs [213]. Acamprosate appears to have an inhibitory effect on glutamate response and modulate NMDAR. The drug also affects K<sup>+</sup>-induced changes in intracellular Ca<sup>2+</sup> concentration, by inhibiting the upregulation of Ca<sup>2+</sup> channels, which is caused by chronic alcohol consumption and states of withdrawal [214]. It promotes abstinence by reestablishing the disturbed balance between GABA and glutamate systems [215]. In contrast to naltrexone, acamprosate is effective only during periods of abstinence. Both pharmaceuticals have been approved and are used in alcohol-dependence treatment. Naltrexone action is related to GSK3 $\beta$  increased activity, whereas acamprosate sustains the activity of Akt (Table 1).

In contrast to anti-craving drugs, disulfiram is associated with an aversive reaction when combined with alcohol. The therapeutic effect of the drug is based on its incompatibility with alcohol. Disulfiram blocks the enzyme aldehyde dehydrogenase, ALDH. Accumulation of acetaldehyde, in the presence of alcohol, usually results in an unpleasant disulfiram-ethanol reaction (DER) consisting of nausea and vomiting. The threat of a DER and negative effects of alcohol consumption results in an avoidance of pain and sickness and consequently increases the effectiveness of the drug [216]. A disulfiram therapy in cocaine and alcohol-dependent individuals supports the effectiveness of cocaine addiction treatment. Disulfiram inhibits dopamine  $\beta$ -hydroxylase (DBH), thus increasing brain dopamine concentrations [217]. The drug seems to have a direct effect on cocaine use and it is not mediated by stopping concurrent alcohol use [218]. Disulfiram appears to be a safe medication, but the treatment needs to be supervised due to DER toxicity. Disulfiram blocks PI3K/Akt pathway (Table 1).

Buprenorphine is an opioid mixed agonist-antagonist, which in treatment is combined with naloxone, due to the risk of abuse [219]. A combination of drugs can be delivered sublingually or by injection and the ratio of buprenorphine to naloxone is 4:1. The drug can be used for pain treatment. Buprenorphine alone and in combination with naloxone are safe and reduce the use and craving for opiates among opiate-addicted patients, thus it was approved for the treatment of opiate addiction [220]. Buprenorphine affects GSK3 $\beta$  via activation of Akt (Table 1).

Varenicline is a partial agonist of nAChR used to treat smoking cessation. The drug affects the  $\alpha 4/\beta 2$  subtype of the receptor and blocks nicotine reward [221]. Varenicline significantly reduces withdrawal and craving symptoms [222] and it shows superior efficacy to bupropion and nicotine patches, whereas bupropion and nicotine patches have similar efficacy [223]. No evidence of increased risk of serious cardiovascular adverse events during or after smoking cessation treatment was observed [224]. In addition, the association with neuropsychiatric adverse events such as suicidality and aggression has not been proven. Varenicline appears to be the most effective single pharmacotherapy available, therefore varenicline and bupropion can be used safely by psychiatrically stable smokers. Varenicline decreases the phosphorylation of GSK3 $\beta$  (Table 1).

Gabapentin is a structural analog of GABA and is used to treat neuropathic pain and inflammation. The anti-epileptic property makes the drug use in chronic agitation and pain therapies for neonates and infants. In adults, gabapentin is widely used to eliminate chemotherapy- and injury-related pain [225]. Gabapentin is also related to alcohol addiction treatment. Alcohol withdrawal syndrome (AWS) is thought to be mediated by GABA and glutamate brain signaling [226]. The drug binds to voltage-sensitive Ca<sup>2+</sup> channels and affects their function [227]. Gabapentin has an influence on GABA and glutamate activity, therefore is effective in the treatment of AWS. It also prevents relapse after medicated alcohol detoxification, in contrast to anti-craving medications, such as naltrexone. Gabapentin activates PI3K/Akt/mTOR pathway (Table 1).

Methadone is a synthetic  $\mu$  OR ( $\mu$ OR) agonist and NMDAR antagonist, which effects are similar to those observed with morphine but much stronger [228]. It is used in the long-term treatment of heroin addiction and for the management of severe pain that does not respond to other treatments [229]. The differences in absorption and metabolism of methadone-maintained individuals make it impossible to establish a diagnostic dose that has an appropriate relationship between its blood concentration and clinical effect [230]. The therapy involves a controlled administration of methadone, thereby stabilization of the opioid-dependent patient. Methadone is expected to activate GSK3 $\beta$  (Table 1).

**Table 1.** Pharmacological substances used in addiction treatment and its impact on GSK3 $\beta$ .

Drug	Molecular Activity	Type of Addiction	Impact on GSK3 $\beta$
Naltrexone	Opioid-agonist	Alcohol	Decreases pSer9 GSK3 $\beta$ amount [227]
Acamprosate	Glutamate receptors antagonist, inhibits upregulation of Ca <sup>2+</sup> channels	Alcohol	Sustains Akt activation [231]
Disulfiram	Blocks the enzyme aldehyde dehydrogenase	Cocaine Alcohol	Inhibits PI3K/Akt/mTOR Pathway [229]
Bupropion	Inhibits the reuptake of monoamine through DAT	Methamphetamine	Inhibits GSK3 $\beta$ [218–220]
Buprenorphine	Opioid agonist-antagonist	Opiate	Activates Akt via ORL-1 receptor [232]
Varenicline	Partial agonist of nAChR	Nicotine	Decreases pSer9 GSK3 $\beta$ <sup>1</sup> [231]
Gabapentin	Influences GABA and glutamate activity	Alcohol	Activates PI3K/Akt/mTOR pathway [233]
Methadone	$\mu$ OR agonist, NMDAR antagonist	Heroin	Decreases pSer9 GSK3 $\beta$ amount <sup>2</sup> [234]

<sup>1</sup> by induced dopamine release. <sup>2</sup> due to opioid exposure.

## 6. Conclusions

GSK3 $\beta$ , despite being engaged in carbohydrates metabolism, is a multifunctional kinase related to many cellular processes. Both, a variety of upstream regulators of GSK3 $\beta$  activity, and a wide spectrum of the kinase substrates place GSK3 $\beta$  at a center point of cellular metabolism regulation and make the kinase a hub linking many signaling pathways. Neurotransmitters and neuromodulators also impact the action of GSK3 $\beta$ , however, the kinase itself can modulate the neurotransmitters receptors responses to its ligands, and is directly engaged in a synaptic potentiation process. Not surprisingly, GSK3 $\beta$  dysregulation has been found to participate in the pathogenesis and progression of major depressive disorder, schizophrenia, and drug addiction. Addiction develops due to a drug-induced malfunctioning of the structures of the reward system, in which one of the main neurotransmitters is DA. Receptors for DA, when activated, influence GSK3 $\beta$  action, moreover, the kinase activity has been observed to be changed in the reward system-related structures during exposure to the drug of abuse. Thus, GSK3 $\beta$  seems to be a promising target for the treatment of addiction.

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## References

- Hughes, K.; Nikolakaki, E.; Plyte, S.E.; Totty, N.F.; Woodgett, J.R. Modulation of the Glycogen Synthase Kinase-3 Family by Tyrosine Phosphorylation. *EMBO J.* **1993**, *12*, 803–808. [[CrossRef](#)] [[PubMed](#)]
- Sutherland, C.; Cohen, P. The  $\alpha$ -Isoform of Glycogen Synthase Kinase-3 from Rabbit Skeletal Muscle Is Inactivated by P70 S6 Kinase or MAP Kinase-Activated Protein Kinase-1 in Vitro. *FEBS Lett.* **1994**, *338*, 37–42. [[CrossRef](#)]
- Brady, M.J.; Bourbonais, F.J.; Saltiel, A.R. The Activation of Glycogen Synthase by Insulin Switches from Kinase Inhibition to Phosphatase Activation during Adipogenesis in 3T3-L1 Cells. *J. Biol. Chem.* **1998**, *273*, 14063–14066. [[CrossRef](#)] [[PubMed](#)]
- Sutherland, C.; Leighton, I.A.; Cohen, P. Inactivation of Glycogen Synthase Kinase-3 $\beta$  by Phosphorylation: New Kinase Connections in Insulin and Growth-Factor Signalling. *Biochem. J.* **1993**, *296*, 15–19. [[CrossRef](#)]
- Tanji, C.; Yamamoto, H.; Yorioka, N.; Kohno, N.; Kikuchi, K.; Kikuchi, A. A-Kinase Anchoring Protein AKAP220 Binds to Glycogen Synthase Kinase-3 $\beta$  (GSK-3 $\beta$ ) and Mediates Protein Kinase A-Dependent Inhibition of GSK-3 $\beta$ . *J. Biol. Chem.* **2002**, *277*, 36955–36961. [[CrossRef](#)]
- Li, M.; Wang, X.; Meintzer, M.K.; Laessig, T.; Birnbaum, M.J.; Heidenreich, K.A. Cyclic AMP Promotes Neuronal Survival by Phosphorylation of Glycogen Synthase Kinase 3beta. *Mol. Cell. Biol.* **2000**, *20*, 9356–9363. [[CrossRef](#)]
- Duda, P.; Wiśniewski, J.; Wójtowicz, T.; Wójcicka, O.; Jaśkiewicz, M.; Drulis-Fajdasz, D.; Rakus, D.; McCubrey, J.A.; Gizak, A. Targeting GSK3 Signaling as a Potential Therapy of Neurodegenerative Diseases and Aging. *Expert Opin. Ther. Targets* **2018**, *22*, 833–848. [[CrossRef](#)]
- Salcedo-Tello, P.; Ortiz-Matamoros, A.; Arias, C. GSK3 Function in the Brain during Development, Neuronal Plasticity, and Neurodegeneration. *J. Alzheimer's Dis.* **2011**, *2011*, 189728. [[CrossRef](#)]
- Takahashi, M.; Tomizawa, K.; Ishiguro, K. Distribution of Tau Protein Kinase I/Glycogen Synthase Kinase-3 $\beta$ , Phosphatases 2A and 2B, and Phosphorylated Tau in the Developing Rat Brain. *Brain Res.* **2000**, *857*, 193–206. [[CrossRef](#)]
- Takahashi, M.; Tomizawa, K.; Kato, R.; Sato, K.; Uchida, T.; Fujita, S.C.; Imahori, K. Localization and Developmental Changes of  $\tau$  Protein Kinase I/Glycogen Synthase Kinase-3 $\beta$  in Rat Brain. *J. Neurochem.* **1994**, *63*, 245–255. [[CrossRef](#)]

11. Mukai, F.; Ishiguro, K.; Sano, Y.; Fujita, S.C. Alternative Splicing Isoform of Tau Protein Kinase I/Glycogen Synthase Kinase 3 $\beta$ . *J. Neurochem.* **2002**, *81*, 1073–1083. [[CrossRef](#)]
12. Trivedi, N.; Marsh, P.; Goold, R.G.; Wood-Kaczmar, A.; Gordon-Weeks, P.R. Glycogen Synthase Kinase-3 $\beta$  Phosphorylation of MAP1B at Ser1260 and Thr1265 Is Spatially Restricted to Growing Axons. *J. Cell. Sci.* **2005**, *118*, 993–1005. [[CrossRef](#)]
13. Goold, R.G.; Gordon-Weeks, P.R. Glycogen Synthase Kinase 3 $\beta$  and the Regulation of Axon Growth. *Biochem. Soc. Trans.* **2004**, *32*, 809–811. [[CrossRef](#)]
14. Castaño, Z.; Gordon-Weeks, P.R.; Kypta, R.M. The Neuron-Specific Isoform of Glycogen Synthase Kinase-3 $\beta$  Is Required for Axon Growth. *J. Neurochem.* **2010**, *113*, 117–130. [[CrossRef](#)]
15. Soutar, M.P.M.; Kim, W.Y.; Williamson, R.; Pegg, M.; Hastie, C.J.; McLauchlan, H.; Snider, W.D.; Gordon-Weeks, P.R.; Sutherland, C. Evidence That Glycogen Synthase Kinase-3 Isoforms Have Distinct Substrate Preference in the Brain. *J. Neurochem.* **2010**, *115*, 974–983. [[CrossRef](#)]
16. Emamian, E. AKT/GSK3 Signaling Pathway and Schizophrenia. *Front. Mol. Neurosci.* **2012**, *5*, 33. [[CrossRef](#)]
17. Denny, C.A.; Heinecke, K.A.; Kim, Y.P.; Baek, R.C.; Loh, K.S.; Butters, T.D.; Bronson, R.T.; Platt, F.M.; Seyfried, T.N. Restricted Ketogenic Diet Enhances the Therapeutic Action of N-Butyldeoxynojirimycin towards Brain GM2 Accumulation in Adult Sandhoff Disease Mice. *J. Neurochem.* **2010**, *113*, 1525–1535. [[CrossRef](#)]
18. Hashizume, T.; Kanematsu, S. Effects of Prostaglandins E2, F2 $\alpha$ , and D2 on the Release of Growth Hormone, Prolactin, and Luteinizing Hormone from Cultured Bovine Anterior Pituitary Cells. *J. Reprod. Dev.* **1995**, *41*, 41–46. [[CrossRef](#)]
19. Beaulieu, J.M.; Sotnikova, T.D.; Gainetdinov, R.R.; Caron, M.G. Paradoxical Striatal Cellular Signaling Responses to Psychostimulants in Hyperactive Mice. *J. Biol. Chem.* **2006**, *281*, 32072–32080. [[CrossRef](#)]
20. Beaulieu, J.M.; Gainetdinov, R.R.; Caron, M.G. Akt/GSK3 Signaling in the Action of Psychotropic Drugs. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 327–347. [[CrossRef](#)]
21. Beaulieu, J.M.; Tirotta, E.; Sotnikova, T.D.; Masri, B.; Salahpour, A.; Gainetdinov, R.R.; Borrelli, E.; Caron, M.G. Regulation of Akt Signaling by D2 and D3 Dopamine Receptors In Vivo. *J. Neurosci.* **2007**, *27*, 881–885. [[CrossRef](#)]
22. Li, Y.C.; Xi, D.; Roman, J.; Huang, Y.Q.; Gao, W.J. Activation of Glycogen Synthase Kinase-3 $\beta$  Is Required for Hyperdopamine and D2 Receptor-Mediated Inhibition of Synaptic NMDA Receptor Function in the Rat Prefrontal Cortex. *J. Neurosci.* **2009**, *29*, 15551. [[CrossRef](#)]
23. Wang, J.R.; Sun, P.H.; Ren, Z.X.; Meltzer, H.Y.; Zhen, X.C. GSK-3 $\beta$  Interacts with Dopamine D1 Receptor to Regulate Receptor Function: Implication for Prefrontal Cortical D1 Receptor Dysfunction in Schizophrenia. *CNS Neurosci. Ther.* **2017**, *23*, 174–187. [[CrossRef](#)]
24. Li, X.; Zhu, W.; Roh, M.S.; Friedman, A.B.; Rosborough, K.; Jope, R.S. In Vivo Regulation of Glycogen Synthase Kinase-3beta (GSK3beta) by Serotonergic Activity in Mouse Brain. *Neuropsychopharmacology* **2004**, *29*, 1426–1431. [[CrossRef](#)]
25. Polter, A.M.; Li, X. Glycogen Synthase Kinase-3 Is an Intermediate Modulator of Serotonin Neurotransmission. *Front. Mol. Neurosci.* **2011**, *4*, 31. [[CrossRef](#)]
26. Lu, F.F.; Su, P.; Liu, F.; Daskalakis, Z.J. Activation of GABAB Receptors Inhibits Protein Kinase B/Glycogen Synthase Kinase 3 Signaling. *Mol. Brain* **2012**, *5*, 41. [[CrossRef](#)]
27. Miller, C.A.; Marshall, J.F. Molecular Substrates for Retrieval and Reconsolidation of Cocaine-Associated Contextual Memory. *Neuron* **2005**, *47*, 873–884. [[CrossRef](#)] [[PubMed](#)]
28. Shiflett, M.W.; Mauna, J.C.; Chipman, A.M.; Peet, E.; Thiels, E. Appetitive Pavlovian Conditioned Stimuli Increase CREB Phosphorylation in the Nucleus Accumbens. *Neurobiol. Learn. Mem.* **2009**, *92*, 451. [[CrossRef](#)]
29. Hur, E.M.; Zhou, F.Q. GSK3 Signaling in Neural Development. *Nat. Rev. Neurosci.* **2010**, *11*, 539–551. [[CrossRef](#)] [[PubMed](#)]
30. Vandesquille, M.; Baudonnat, M.; Decorte, L.; Louis, C.; Lestage, P.; Béracochéa, D. Working Memory Deficits and Related Disinhibition of the CAMP/PKA/CREB Are Alleviated by Prefrontal A4 $\beta$ 2\*-NACHRs Stimulation in Aged Mice. *Neurobiol. Aging* **2013**, *34*, 1599–1609. [[CrossRef](#)]
31. Parsons, R.G.; Gafford, G.M.; Helmstetter, F.J. Translational Control via the Mammalian Target of Rapamycin Pathway Is Critical for the Formation and Stability of Long-Term Fear Memory in Amygdala Neurons. *J. Neurosci.* **2006**, *26*, 12977–12983. [[CrossRef](#)] [[PubMed](#)]
32. Stoica, L.; Zhu, P.J.; Huang, W.; Zhou, H.; Kozma, S.C.; Costa-Mattoli, M. Selective Pharmacogenetic Inhibition of Mammalian Target of Rapamycin Complex I (MTORC1) Blocks Long-Term Synaptic Plasticity and Memory Storage. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 3791–3796. [[CrossRef](#)] [[PubMed](#)]
33. Hay, N.; Sonenberg, N. Upstream and Downstream of MTOR. *Genes Dev.* **2004**, *18*, 1926–1945. [[CrossRef](#)]
34. Ma, X.M.; Blenis, J. Molecular Mechanisms of MTOR-Mediated Translational Control. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 307–318. [[CrossRef](#)]
35. Wu, D.; Pan, W. GSK3: A Multifaceted Kinase in Wnt Signaling. *Trends Biochem. Sci.* **2010**, *35*, 161. [[CrossRef](#)]
36. Doble, B.W.; Patel, S.; Wood, G.A.; Kockeritz, L.K.; Woodgett, J.R. Functional Redundancy of GSK-3alpha and GSK-3beta in Wnt/Beta-Catenin Signaling Shown by Using an Allelic Series of Embryonic Stem Cell Lines. *Dev. Cell* **2007**, *12*, 957–971. [[CrossRef](#)]
37. Liu, X.; Rubin, J.S.; Kimmel, A.R. Rapid, Wnt-Induced Changes in GSK3beta Associations That Regulate Beta-Catenin Stabilization Are Mediated by Alpha Proteins. *Curr. Biol.* **2005**, *15*, 1989–1997. [[CrossRef](#)]



38. Mao, Y.; Ge, X.; Frank, C.L.; Madison, J.M.; Koehler, A.N.; Doud, M.K.; Tassa, C.; Berry, E.M.; Soda, T.; Singh, K.K.; et al. Disrupted in Schizophrenia 1 Regulates Neuronal Progenitor Proliferation via Modulation of GSK3 $\beta$ / $\beta$ -Catenin Signaling. *Cell* **2009**, *136*, 1017–1031. [[CrossRef](#)]
39. Young, C.S.; Kitamura, M.; Hardy, S.; Kitajewski, J. Wnt-1 Induces Growth, Cytosolic Beta-Catenin, and Tcf/Lef Transcriptional Activation in Rat-1 Fibroblasts. *Mol. Cell. Biol.* **1998**, *18*, 2474–2485. [[CrossRef](#)]
40. Orford, K.; Crockett, C.; Jensen, J.P.; Weissman, A.M.; Byers, S.W. Serine Phosphorylation-Regulated Ubiquitination and Degradation of Beta-Catenin. *J. Biol. Chem.* **1997**, *272*, 24735–24738. [[CrossRef](#)]
41. Miller, J.R.; Moon, R.T. Signal Transduction through Beta-Catenin and Specification of Cell Fate during Embryogenesis. *Genes Dev.* **1996**, *10*, 2527–2539. [[CrossRef](#)]
42. Im, H.I.; Kenny, P.J. MicroRNAs in Neuronal Function and Dysfunction. *Trends Neurosci.* **2012**, *35*, 325–334. [[CrossRef](#)]
43. Ballou, L.M.; Tian, P.Y.; Lin, H.Y.; Jiang, Y.P.; Lin, R.Z. Dual Regulation of Glycogen Synthase Kinase-3beta by the Alpha1A-Adrenergic Receptor. *J. Biol. Chem.* **2001**, *276*, 40910–40916. [[CrossRef](#)]
44. Xing, B.; Li, Y.C.; Gao, W.J. Norepinephrine versus Dopamine and Their Interaction in Modulating Synaptic Function in the Prefrontal Cortex. *Brain Res.* **2016**, *1641*, 217. [[CrossRef](#)]
45. Morioka, N.; Kodama, K.; Tsuruta, M.; Hashizume, H.; Kochi, T.; Nakamura, Y.; Zhang, F.F.; Hisaoka-Nakashima, K. Stimulation of Nuclear Receptor REV-ERBs Suppresses Inflammatory Responses in Spinal Microglia. *Neurochem. Int.* **2021**, *151*, 105216. [[CrossRef](#)]
46. Luo, H.R.; Hattori, H.; Hossain, M.A.; Hester, L.; Huang, Y.; Lee-Kwon, W.; Donowitz, M.; Nagata, E.; Snyder, S.H. Akt as a Mediator of Cell Death. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 11712–11717. [[CrossRef](#)]
47. Szatmari, E.; Habas, A.; Yang, P.; Zheng, J.J.; Hagg, T.; Hetman, M. A Positive Feedback Loop between Glycogen Synthase Kinase 3beta and Protein Phosphatase 1 after Stimulation of NR2B NMDA Receptors in Forebrain Neurons. *J. Biol. Chem.* **2005**, *280*, 37526–37535. [[CrossRef](#)]
48. Chen, P.; Gu, Z.; Liu, W.; Yan, Z. Glycogen Synthase Kinase 3 Regulates N-Methyl-D-Aspartate Receptor Channel Trafficking and Function in Cortical Neurons. *Mol. Pharmacol.* **2007**, *72*, 40–51. [[CrossRef](#)]
49. Deng, Y.; Xiong, Z.; Chen, P.; Wei, J.; Chen, S.; Yan, Z.  $\beta$ -Amyloid Impairs the Regulation of N-Methyl-D-Aspartate Receptors by Glycogen Synthase Kinase 3. *Neurobiol. Aging* **2014**, *35*, 449–459. [[CrossRef](#)]
50. Li, L.; Stefan, M.I.; le Novère, N. Calcium Input Frequency, Duration and Amplitude Differentially Modulate the Relative Activation of Calcineurin and CaMKII. *PLoS ONE* **2012**, *7*, e43810. [[CrossRef](#)] [[PubMed](#)]
51. Song, B.; Lai, B.; Zheng, Z.; Zhang, Y.; Luo, J.; Wang, C.; Chen, Y.; Woodgett, J.R.; Li, M. Inhibitory Phosphorylation of GSK-3 by CaMKII Couples Depolarization to Neuronal Survival. *J. Biol. Chem.* **2010**, *285*, 41122–41134. [[CrossRef](#)] [[PubMed](#)]
52. Kim, Y.; Lee, Y.; Seo, M.; Kim, S.Y.; Lee, J.E.; Youn, H.D.; Kim, Y.S.; Juhn, Y.S. Calcineurin Dephosphorylates Glycogen Synthase Kinase-3 Beta at Serine-9 in Neuroblast-Derived Cells. *J. Neurochem.* **2009**, *111*, 344–354. [[CrossRef](#)] [[PubMed](#)]
53. Liu, S.J.; Zukin, R.S. Ca<sup>2+</sup>-Permeable AMPA Receptors in Synaptic Plasticity and Neuronal Death. *Trends Neurosci.* **2007**, *30*, 126–134. [[CrossRef](#)] [[PubMed](#)]
54. Bats, C.; Groc, L.; Choquet, D. The Interaction between Stargazin and PSD-95 Regulates AMPA Receptor Surface Trafficking. *Neuron* **2007**, *53*, 719–734. [[CrossRef](#)]
55. Wei, J.; Liu, W.; Yan, Z. Regulation of AMPA Receptor Trafficking and Function by Glycogen Synthase Kinase 3. *J. Biol. Chem.* **2010**, *285*, 26369–26376. [[CrossRef](#)]
56. Doble, B.W.; Woodgett, J.R. GSK-3: Tricks of the Trade for a Multi-Tasking Kinase. *J. Cell Sci.* **2003**, *116*, 1175–1186. [[CrossRef](#)]
57. Duda, P.; Hajka, D.; Wójcicka, O.; Rakus, D.; Gizak, A. GSK3 $\beta$ : A Master Player in Depressive Disorder Pathogenesis and Treatment Responsiveness. *Cells* **2020**, *9*, 727. [[CrossRef](#)]
58. Balsi, G.; Napolitano, F.; Ursini, G.; Di Giorgio, A.; Caforio, G.; Taurisano, P.; Fazio, L.; Gelao, B.; Attorotto, M.T.; Colagiorgio, L.; et al. Association of GSK-3 $\beta$  Genetic Variation with GSK-3 $\beta$  Expression, Prefrontal Cortical Thickness, Prefrontal Physiology, and Schizophrenia. *Am. J. Psychiatry* **2013**, *170*, 868–876. [[CrossRef](#)]
59. Khan, I.; Tantray, M.A.; Alam, M.A.S.; Hamid, H. Natural and Synthetic Bioactive Inhibitors of Glycogen Synthase Kinase. *Eur. J. Med. Chem.* **2017**, *125*, 464–477. [[CrossRef](#)]
60. Olds, J.; Milner, P. Positive Reinforcement Produced by Electrical Stimulation of Septal Area and Other Regions of Rat Brain. *J. Comp. Physiol. Psychol.* **1954**, *47*, 419–427. [[CrossRef](#)]
61. Ferenczi, E.A.; Zalocusky, K.A.; Liston, C.; Grosenick, L.; Warden, M.R.; Amatya, D.; Katovich, K.; Mehta, H.; Patenaude, B.; Ramakrishnan, C.; et al. Prefrontal Cortical Regulation of Brainwide Circuit Dynamics and Reward-Related Behavior. *Science* **2016**, *351*, 6268. [[CrossRef](#)]
62. Drugs, Brains, and Behavior: The Science of Addiction: Preface | NIDA. Available online: <https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/preface> (accessed on 13 November 2021).
63. Robbins, T.W.; Everitt, B.J. Limbic-Striatal Memory Systems and Drug Addiction. *Neurobiol. Learn. Mem.* **2002**, *78*, 625–636. [[CrossRef](#)]
64. Mitchell, J.M.; O’Neil, J.P.; Janabi, M.; Marks, S.M.; Jagust, W.J.; Fields, H.L. Alcohol Consumption Induces Endogenous Opioid Release in the Human Orbitofrontal Cortex and Nucleus Accumbens. *Sci. Transl. Med.* **2012**, *4*. [[CrossRef](#)]
65. Wise, R.A. Roles for Nigrostriatal–Not Just Mesocorticolimbic—Dopamine in Reward and Addiction. *Trends Neurosci.* **2009**, *32*, 517–524. [[CrossRef](#)]

66. Volkow, N.D.; Wang, G.J.; Telang, F.; Fowler, J.S.; Logan, J.; Jayne, M.; Ma, Y.; Pradhan, K.; Wong, C. Profound Decreases in Dopamine Release in Striatum in Detoxified Alcoholics: Possible Orbitofrontal Involvement. *J. Neurosci.* **2007**, *27*, 12700–12706. [[CrossRef](#)]
67. Wise, R.A.; Bozarth, M.A. Brain Reward Circuitry: Four Circuit Elements “Wired” in Apparent Series. *Brain Res. Bulletin* **1984**, *12*, 203–208. [[CrossRef](#)]
68. Gallistel, C.R.; Shizgal, P.; Yeomans, J.S. A Portrait of the Substrate for Self-Stimulation. *Psychol. Rev.* **1981**, *88*, 228–273. [[CrossRef](#)]
69. Gardner, E.L. Addiction and Brain Reward and Antireward Pathways. *Adv. Psychosom. Med.* **2011**, *30*, 22–60. [[CrossRef](#)]
70. Alheid, G.F.; Heimer, L. New Perspectives in Basal Forebrain Organization of Special Relevance for Neuropsychiatric Disorders: The Striatopallidal, Amygdaloid, and Corticopetal Components of Substantia Innominata. *Neuroscience* **1988**, *27*, 1–39. [[CrossRef](#)]
71. Wise, R.A. Addictive Drugs and Brain Stimulation Reward. *Annu. Rev. Neurosci.* **1996**, *19*, 319–340. [[CrossRef](#)]
72. McBride, W.J.; Murphy, J.M.; Ikemoto, S. Localization of Brain Reinforcement Mechanisms: Intracranial Self-Administration and Intracranial Place-Conditioning Studies. *Behav. Brain Res.* **1999**, *101*, 129–152. [[CrossRef](#)]
73. Nauta, W.J.H.; Mehler, W.R. Projections of the Lentiform Nucleus in the Monkey. *Brain Res.* **1966**, *1*, 3–42. [[CrossRef](#)]
74. Lammel, S.; Lim, B.K.; Malenka, R.C. Reward and Aversion in a Heterogeneous Midbrain Dopamine System. *Neuropharmacology* **2014**, *76 Pt B*, 351–359. [[CrossRef](#)]
75. Lammel, S.; Hetzel, A.; Häckel, O.; Jones, I.; Liss, B.; Roeper, J. Unique Properties of Mesoprefrontal Neurons within a Dual Mesocorticolimbic Dopamine System. *Neuron* **2008**, *57*, 760–773. [[CrossRef](#)]
76. Steinberg, E.E.; Boivin, J.R.; Saunders, B.T.; Witten, I.B.; Deisseroth, K.; Janak, P.H. Positive Reinforcement Mediated by Midbrain Dopamine Neurons Requires D1 and D2 Receptor Activation in the Nucleus Accumbens. *PLoS ONE* **2014**, *9*, e94771. [[CrossRef](#)]
77. Phelps, E.A. Human Emotion and Memory: Interactions of the Amygdala and Hippocampal Complex. *Curr. Opin. Neurobiol.* **2004**, *14*, 198–202. [[CrossRef](#)]
78. Stephan, K.E.; Bach, D.R.; Fletcher, P.C.; Flint, J.; Frank, M.J.; Friston, K.J.; Heinz, A.; Huys, Q.J.M.; Owen, M.J.; Binder, E.B.; et al. Charting the Landscape of Priority Problems in Psychiatry, Part 1: Classification and Diagnosis. *Lancet Psychiatry* **2016**, *3*, 77–83. [[CrossRef](#)]
79. Gardner, E.L. What We Have Learned about Addiction from Animal Models of Drug Self-Administration. *Am. J. Addict.* **2000**, *9*, 285–313. [[CrossRef](#)] [[PubMed](#)]
80. Anagnostaras, S.G.; Robinson, T.E. Sensitization to the Psychomotor Stimulant Effects of Amphetamine: Modulation by Associative Learning. *Behav. Neurosci.* **1996**, *110*, 1397–1414. [[CrossRef](#)] [[PubMed](#)]
81. Badiani, A.; Anagnostaras, S.G.; Robinson, T.E. The Development of Sensitization to the Psychomotor Stimulant Effects of Amphetamine Is Enhanced in a Novel Environment. *Psychopharmacology* **1995**, *117*, 443–452. [[CrossRef](#)] [[PubMed](#)]
82. Nestler, E.J. Under Siege: The Brain on Opiates. *Neuron* **1996**, *16*, 897–900. [[CrossRef](#)]
83. Hope, B.T.; Nye, H.E.; Kelz, M.B.; Self, D.W.; Iadarola, M.J.; Nakabeppu, Y.; Duman, R.S.; Nestler, E.J. Induction of a Long-Lasting AP-1 Complex Composed of Altered Fos-like Proteins in Brain by Chronic Cocaine and Other Chronic Treatments. *Neuron* **1994**, *13*, 1235–1244. [[CrossRef](#)]
84. Koob, G.F.; Le Moal, M. Plasticity of Reward Neurocircuitry and the “dark Side” of Drug Addiction. *Nat. Neurosci.* **2005**, *8*, 1442–1444. [[CrossRef](#)]
85. Gerfen, C.R.; Engber, T.M.; Mahan, L.C.; Susel, Z.; Chase, T.N.; Monsma, F.J.; Sibley, D.R. D1 and D2 Dopamine Receptor-Regulated Gene Expression of Striatonigral and Striatopallidal Neurons. *Science* **1990**, *250*, 1429–1432. [[CrossRef](#)]
86. Lobo, M.K.; Covington, H.E.; Chaudhury, D.; Friedman, A.K.; Sun, H.S.; Damez-Werno, D.; Dietz, D.M.; Zaman, S.; Koo, J.W.; Kennedy, P.J.; et al. Cell Type-Specific Loss of BDNF Signaling Mimics Optogenetic Control of Cocaine Reward. *Science* **2010**, *330*, 385–390. [[CrossRef](#)]
87. Volkow, N.D.; Fowler, J.S.; Wang, G.-J.; Hitzemann, R.; Logan, J.; Schlyer, D.J.; Dewey, S.L.; Wolf, A.P. Decreased Dopamine D2 Receptor Availability Is Associated with Reduced Frontal Metabolism in Cocaine Abusers. *Synapse* **1993**, *14*, 169–177. [[CrossRef](#)]
88. Davey, C.G.; Yücel, M.; Allen, N.B. The Emergence of Depression in Adolescence: Development of the Prefrontal Cortex and the Representation of Reward. *Neurosci. Biobehav. Rev.* **2008**, *32*, 1–19. [[CrossRef](#)]
89. Schultz, W.; Dayan, P.; Montague, P.R. A Neural Substrate of Prediction and Reward. *Science* **1997**, *275*, 1593–1599. [[CrossRef](#)]
90. Waelti, P.; Dickinson, A.; Schultz, W. Dopamine Responses Comply with Basic Assumptions of Formal Learning Theory. *Nature* **2001**, *412*, 43–48. [[CrossRef](#)]
91. Garbusow, M.; Schad, D.J.; Sebold, M.; Friedel, E.; Bernhardt, N.; Koch, S.P.; Steinacher, B.; Kathmann, N.; Geurts, D.E.M.; Sommer, C.; et al. Pavlovian-to-Instrumental Transfer Effects in the Nucleus Accumbens Relate to Relapse in Alcohol Dependence. *Addict. Biol.* **2016**, *21*, 719–731. [[CrossRef](#)]
92. LeBlanc, K.H.; Ostlund, S.B.; Maidment, N.T. Pavlovian-to-Instrumental Transfer in Cocaine Seeking Rats. *Behav. Neurosci.* **2012**, *126*, 681–689. [[CrossRef](#)] [[PubMed](#)]
93. Nestler, E.J.; Barrot, M.; Self, D.W. DeltaFosB: A Sustained Molecular Switch for Addiction. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 11042–11046. [[CrossRef](#)] [[PubMed](#)]
94. Hyman, S.E.; Malenka, R.C. Addiction and the Brain: The Neurobiology of Compulsion and Its Persistence. *Nat. Rev. Neurosci.* **2001**, *2*, 695–703. [[CrossRef](#)] [[PubMed](#)]
95. Werme, M.; Messer, C.; Olson, L.; Gilden, L.; Thorén, P.; Nestler, E.J.; Brené, S. Delta FosB Regulates Wheel Running. *J. Neurosci.* **2002**, *22*, 8133–8138. [[CrossRef](#)]

96. Kelz, M.B.; Chen, J.; Carlezon, W.A.; Whisler, K.; Gilden, L.; Beckmann, A.M.; Steffen, C.; Zhang, Y.J.; Marotti, L.; Self, D.W.; et al. Expression of the Transcription Factor DeltaFosB in the Brain Controls Sensitivity to Cocaine. *Nature* **1999**, *401*, 272–276. [[CrossRef](#)]
97. Teegarden, S.L.; Nestler, E.J.; Bale, T.L. Delta FosB-Mediated Alterations in Dopamine Signaling Are Normalized by a Palatable High-Fat Diet. *Biol. Psychiatry* **2008**, *64*, 941–950. [[CrossRef](#)]
98. Teegarden, S.L.; Bale, T.L. Decreases in Dietary Preference Produce Increased Emotionality and Risk for Dietary Relapse. *Biol. Psychiatry* **2007**, *61*, 1021–1029. [[CrossRef](#)]
99. Dobrazanski, P.; Noguchi, T.; Kovary, K.; Rizzo, C.A.; Lazo, P.S.; Bravo, R. Both Products of the FosB Gene, FosB and Its Short Form, FosB/SF, Are Transcriptional Activators in Fibroblasts. *Mol. Cell. Biol.* **1991**, *11*, 5470–5478. [[CrossRef](#)]
100. White, F.J.; Hu, X.T.; Zhang, X.F.; Wolf, M.E. Repeated Administration of Cocaine or Amphetamine Alters Neuronal Responses to Glutamate in the Mesoaccumbens Dopamine System. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 445–454.
101. Carlezon, W.A.; Thome, J.; Olson, V.G.; Lane-Ladd, S.B.; Brodtkin, E.S.; Hiroi, N.; Duman, R.S.; Neve, R.L.; Nestler, E.J. Regulation of Cocaine Reward by CREB. *Science* **1998**, *282*, 2272–2275. [[CrossRef](#)]
102. Todtenkopf, M.S.; Marcus, J.F.; Portoghesse, P.S.; Carlezon, W.A. Effects of Kappa-Opioid Receptor Ligands on Intracranial Self-Stimulation in Rats. *Psychopharmacology* **2004**, *172*, 463–470. [[CrossRef](#)]
103. Svensson, P.; Hurd, Y.L. Specific Reductions of Striatal Prodynorphin and D1 Dopamine Receptor Messenger RNAs during Cocaine Abstinence. *Brain Res. Mol. Brain Res.* **1998**, *56*, 162–168. [[CrossRef](#)]
104. Uhl, G.R. Molecular Genetics of Substance Abuse Vulnerability: Remarkable Recent Convergence of Genome Scan Results. *Ann. N. Y. Acad. Sci.* **2004**, *1025*, 1–13. [[CrossRef](#)]
105. Uhl, G.R.; Drgon, T.; Johnson, C.; Fatusin, O.O.; Liu, Q.R.; Contoreggi, C.; Li, C.Y.; Buck, K.; Crabbe, J. “Higher Order” Addiction Molecular Genetics: Convergent Data from Genome-Wide Association in Humans and Mice. *Biochem. Pharmacol.* **2008**, *75*, 98–111. [[CrossRef](#)]
106. Rennels, M.L.; Gregory, T.F.; Blaumanis, O.R.; Fujimoto, K.; Grady, P.A. Evidence for a ‘Paravascular’ Fluid Circulation in the Mammalian Central Nervous System, Provided by the Rapid Distribution of Tracer Protein throughout the Brain from the Subarachnoid Space. *Brain Res.* **1985**, *326*, 47–63. [[CrossRef](#)]
107. Blum, K.; Braverman, E.R.; Holder, J.M.; Lubar, J.F.; Monastra, V.I.; Miller, D.; Lubar, J.O.; Chen, T.J.H.; Comings, D.E. Reward Deficiency Syndrome: A Biogenetic Model for the Diagnosis and Treatment of Impulsive, Addictive, and Compulsive Behaviors. *J. Psychoact. Drugs* **2000**, *32* (Suppl. 1), 1–112. [[CrossRef](#)]
108. Comings, D.E.; Blum, K. Reward Deficiency Syndrome: Genetic Aspects of Behavioral Disorders. *Prog. Brain Res.* **2000**, *126*, 325–341. [[CrossRef](#)]
109. Blum, K.; Sheridan, P.J.; Wood, R.C.; Braverman, E.R.; Chen, T.J.H.; Cull, J.G.; Comings, D.E. The D2 Dopamine Receptor Gene as a Determinant of Reward Deficiency Syndrome. *J. R. Soc. Med.* **1996**, *89*, 396. [[CrossRef](#)]
110. Leroy, K.; Brion, J.P. Developmental Expression and Localization of Glycogen Synthase Kinase-3beta in Rat Brain. *J. Chem. Neuroanat.* **1999**, *16*, 279–293. [[CrossRef](#)]
111. Latapy, C.; Rioux, V.; Guitton, M.J.; Beaulieu, J.M. Selective Deletion of Forebrain Glycogen Synthase Kinase 3β Reveals a Central Role in Serotonin-Sensitive Anxiety and Social Behaviour. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2012**, *367*, 2460–2474. [[CrossRef](#)]
112. Pandey, G.N.; Dwivedi, Y.; Rizavi, H.S.; Teppen, T.; Gaszner, G.L.; Roberts, R.C.; Conley, R.R. GSK-3beta Gene Expression in Human Postmortem Brain: Regional Distribution, Effects of Age and Suicide. *Neurochem. Res.* **2009**, *34*, 274–285. [[CrossRef](#)]
113. Wilkinson, M.B.; Dias, C.; Magida, J.; Mazei-Robison, M.; Lobo, M.; Kennedy, P.; Dietz, D.; Covington, H.; Russo, S.; Neve, R.; et al. A Novel Role of the WNT-Dishevelled-GSK3β Signaling Cascade in the Mouse Nucleus Accumbens in a Social Defeat Model of Depression. *J. Neurosci.* **2011**, *31*, 9084–9092. [[CrossRef](#)] [[PubMed](#)]
114. Lucas, J.J.; Hernández, F.; Gómez-Ramos, P.; Morán, M.A.; Hen, R.; Avila, J. Decreased Nuclear Beta-Catenin, Tau Hyperphosphorylation and Neurodegeneration in GSK-3beta Conditional Transgenic Mice. *EMBO J.* **2001**, *20*, 27–39. [[CrossRef](#)] [[PubMed](#)]
115. Spittaels, K.; van den Haute, C.; van Dorpe, J.; Terwel, D.; Vandezande, K.; Lasrado, R.; Bruynseels, K.; Irizarry, M.; Verhoye, M.; van Lint, J.; et al. Neonatal Neuronal Overexpression of Glycogen Synthase Kinase-3 Beta Reduces Brain Size in Transgenic Mice. *Neuroscience* **2002**, *113*, 797–808. [[CrossRef](#)]
116. Tan, M.; Ma, S.; Huang, Q.; Hu, K.; Song, B.; Li, M. GSK-3α/β-Mediated Phosphorylation of CRMP-2 Regulates Activity-Dependent Dendritic Growth. *J. Neurochem.* **2013**, *125*, 685–697. [[CrossRef](#)]
117. Rippin, I.; Eldar-Finkelman, H. Mechanisms and Therapeutic Implications of GSK-3 in Treating Neurodegeneration. *Cells* **2021**, *10*, 262. [[CrossRef](#)]
118. Yoshimura, T.; Kawano, Y.; Arimura, N.; Kawabata, S.; Kikuchi, A.; Kaibuchi, K. GSK-3beta Regulates Phosphorylation of CRMP-2 and Neuronal Polarity. *Cell* **2005**, *120*, 137–149. [[CrossRef](#)]
119. Shi, X.; Barr, J.L.; von Weltin, E.; Wolsh, C.; Unterwald, E.M. Differential Roles of Accumbal GSK3 β in Cocaine versus Morphine-Induced Place Preference, U50,488H-Induced Place Aversion, and Object Memory. *J. Pharmacol. Exp. Ther.* **2019**, *371*, 339–347. [[CrossRef](#)]
120. Xu, C.M.; Wang, J.; Wu, P.; Zhu, W.L.; Li, Q.Q.; Xue, Y.X.; Zhai, H.F.; Shi, J.; Lu, L. Glycogen Synthase Kinase 3beta in the Nucleus Accumbens Core Mediates Cocaine-Induced Behavioral Sensitization. *J. Neurochem.* **2009**, *111*, 1357–1368. [[CrossRef](#)]

121. Crofton, E.J.; Nenov, M.N.; Zhang, Y.; Scala, F.; Page, S.A.; McCue, D.L.; Li, D.; Hommel, J.D.; Laezza, F.; Green, T.A. Glycogen Synthase Kinase 3 Beta Alters Anxiety-, Depression-, and Addiction-Related Behaviors and Neuronal Activity in the Nucleus Accumbens Shell. *Neuropharmacology* **2017**, *117*, 49–60. [[CrossRef](#)]
122. Du, J.; Wei, Y.; Liu, L.; Wang, Y.; Khairova, R.; Blumenthal, R.; Tragon, T.; Hunsberger, J.G.; Machado-Vieira, R.; Drevets, W.; et al. A Kinesin Signaling Complex Mediates the Ability of GSK-3beta to Affect Mood-Associated Behaviors. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 11573–11578. [[CrossRef](#)]
123. Hooper, C.; Markevich, V.; Plattner, F.; Killick, R.; Schofield, E.; Engel, T.; Hernandez, F.; Anderton, B.; Rosenblum, K.; Bliss, T.; et al. Glycogen Synthase Kinase-3 Inhibition Is Integral to Long-Term Potentiation. *Eur. J. Neurosci* **2007**, *25*, 81–86. [[CrossRef](#)]
124. Peineau, S.; Taghibiglou, C.; Bradley, C.; Wong, T.P.; Liu, L.; Lu, J.; Lo, E.; Wu, D.; Saule, E.; Bouschet, T.; et al. LTP Inhibits LTD in the Hippocampus via Regulation of GSK3beta. *Neuron* **2007**, *53*, 703–717. [[CrossRef](#)]
125. Mulkey, R.M.; Endo, S.; Shenolikar, S.; Malenka, R.C. Involvement of a Calcineurin/Inhibitor-1 Phosphatase Cascade in Hippocampal Long-Term Depression. *Nature* **1994**, *369*, 486–488. [[CrossRef](#)]
126. Zhu, L.Q.; Wang, S.H.; Liu, D.; Yin, Y.Y.; Tian, Q.; Wang, X.C.; Wang, Q.; Chen, J.G.; Wang, J.Z. Activation of Glycogen Synthase Kinase-3 Inhibits Long-Term Potentiation with Synapse-Associated Impairments. *J. Neurosci.* **2007**, *27*, 12211–12220. [[CrossRef](#)]
127. Hernández, F.; Borrell, J.; Guaza, C.; Avila, J.; Lucas, J.J. Spatial Learning Deficit in Transgenic Mice That Conditionally Over-Express GSK-3beta in the Brain but Do Not Form Tau Filaments. *J. Neurochem.* **2002**, *83*, 1529–1533. [[CrossRef](#)]
128. Kimura, T.; Yamashita, S.; Nakao, S.; Park, J.M.; Murayama, M.; Mizoroki, T.; Yoshiike, Y.; Sahara, N.; Takashima, A. GSK-3beta Is Required for Memory Reconsolidation in Adult Brain. *PLoS ONE* **2008**, *3*, e3540. [[CrossRef](#)]
129. Jope, R.S.; Cheng, Y.; Lowell, J.A.; Worthen, R.J.; Sitbon, Y.H.; Beurel, E. Stressed and Inflamed, Can GSK3 Be Blamed? *Trends Biochem. Sci.* **2017**, *42*, 180–192. [[CrossRef](#)]
130. Brami-Cherrier, K.; Valjent, E.; Garcia, M.; Pagès, C.; Hipskind, R.A.; Caboche, J. Dopamine Induces a PI3-Kinase-Independent Activation of Akt in Striatal Neurons: A New Route to CAMP Response Element-Binding Protein Phosphorylation. *J. Neurosci.* **2002**, *22*, 8911–8921. [[CrossRef](#)]
131. Beaulieu, J.M.; Sotnikova, T.D.; Yao, W.D.; Kockeritz, L.; Woodgett, J.R.; Gainetdinov, R.R.; Caron, M.G. Lithium Antagonizes Dopamine-Dependent Behaviors Mediated by an AKT/Glycogen Synthase Kinase 3 Signaling Cascade. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5099–5104. [[CrossRef](#)]
132. Beaulieu, J.M.; Sotnikova, T.D.; Marion, S.; Lefkowitz, R.J.; Gainetdinov, R.R.; Caron, M.G. An Akt/Beta-Arrestin 2/PP2A Signaling Complex Mediates Dopaminergic Neurotransmission and Behavior. *Cell* **2005**, *122*, 261–273. [[CrossRef](#)] [[PubMed](#)]
133. Urs, N.M.; Daigle, T.L.; Caron, M.G. A Dopamine D1 Receptor-Dependent  $\beta$ -Arrestin Signaling Complex Potentially Regulates Morphine-Induced Psychomotor Activation but Not Reward in Mice. *Neuropsychopharmacology* **2011**, *36*, 551–558. [[CrossRef](#)] [[PubMed](#)]
134. Salles, M.J.; Hervé, D.; Rivet, J.M.; Longueville, S.; Millan, M.J.; Girault, J.A.; Cour, C.M.L. Transient and Rapid Activation of Akt/GSK-3 $\beta$  and MTORC1 Signaling by D3 Dopamine Receptor Stimulation in Dorsal Striatum and Nucleus Accumbens. *J. Neurochem.* **2013**, *125*, 532–544. [[CrossRef](#)] [[PubMed](#)]
135. La Cour, C.M.; Salles, M.J.; Pasteau, V.; Millan, M.J. Signaling Pathways Leading to Phosphorylation of Akt and GSK-3 $\beta$  by Activation of Cloned Human and Rat Cerebral D<sub>2</sub> and D<sub>3</sub> Receptors. *Mol. Pharmacol.* **2011**, *79*, 91–105. [[CrossRef](#)]
136. Li, S.X.; Wei, Y.M.; Shi, H.S.; Luo, Y.X.; Ding, Z.B.; Xue, Y.X.; Lu, L.; Yu, C.X. Glycogen Synthase Kinase-3 $\beta$  in the Ventral Tegmental Area Mediates Diurnal Variations in Cocaine-Induced Conditioned Place Preference in Rats. *Addict. Biol.* **2014**, *19*, 996–1005. [[CrossRef](#)]
137. Khlghatyan, J.; Khlghatyan, J.; Beaulieu, J.M. CRISPR-Cas9-Mediated Intersectional Knockout of Glycogen Synthase Kinase 3 $\beta$  in D2 Receptor-Expressing Medial Prefrontal Cortex Neurons Reveals Contributions to Emotional Regulation. *CRISPR J.* **2020**, *3*, 198–210. [[CrossRef](#)]
138. Fatahi, Z.; Zeinaddini-Meymand, A.; Karimi-Haghighi, S.; Moradi, M.; Khodaghali, F.; Haghparast, A. Naloxone-Precipitated Withdrawal Ameliorates Impairment of Cost-Benefit Decision Making in Morphine-Treated Rats: Involvement of BDNF, p-GSK3- $\beta$ , and p-CREB in the Amygdala. *Neurobiol. Learn. Mem.* **2020**, *167*, 107138. [[CrossRef](#)]
139. White, N.M. Addictive Drugs as Reinforcers: Multiple Partial Actions on Memory Systems. *Addiction* **1996**, *91*, 921–950. [[CrossRef](#)]
140. Packard, M.G.; Teather, L.A. Amygdala Modulation of Multiple Memory Systems: Hippocampus and Caudate- Putamen. *Neurobiol. Learn. Mem.* **1998**, *69*, 163–203. [[CrossRef](#)]
141. Udo, T.; Ugalde, F.; DiPietro, N.; Eichenbaum, H.B.; Kantak, K.M. Effect of Persistent Cocain Self-Administration on Amygdala-Dependent and Dorsal Striatum-Dependent Learning in Rats. *Psychopharmacology* **2004**, *174*, 237–245. [[CrossRef](#)]
142. Dickinson, A.; Wood, N.; Smith, J.W. Alcohol Seeking by Rats: Action or Habit? *Q. J. Exp. Psychol* **2002**, *55*, 331–348. [[CrossRef](#)]
143. Wood, S.C.; Fay, J.; Sage, J.R.; Anagnostaras, S.G. Cocaine and Pavlovian Fear Conditioning: Dose-Effect Analysis. *Behav. Brain Res.* **2007**, *176*, 244–250. [[CrossRef](#)]
144. Wood, S.C.; Anagnostaras, S.G. Memory and Psychostimulants: Modulation of Pavlovian Fear Conditioning by Amphetamine in C57BL/6 Mice. *Psychopharmacology* **2009**, *202*, 197–206. [[CrossRef](#)]
145. Iñiguez, S.D.; Charntikov, S.; Baella, S.A.; Herbert, M.S.; Bolaños-Guzmán, C.A.; Crawford, C.A. Post-Training Cocaine Exposure Facilitates Spatial Memory Consolidation in C57BL/6 Mice. *Hippocampus* **2012**, *22*, 802–813. [[CrossRef](#)]
146. Leri, F.; Nahas, E.; Henderson, K.; Limebeer, C.L.; Parker, L.A.; White, N.M. Effects of Post-Training Heroin and d-Amphetamine on Consolidation of Win-Stay Learning and Fear Conditioning. *J. Psychopharmacol.* **2013**, *27*, 292–301. [[CrossRef](#)]

147. DePoy, L.; Daut, R.; Brigman, J.L.; MacPherson, K.; Crowley, N.; Gunduz-Cinar, O.; Pickens, C.L.; Cinar, R.; Saksida, L.M.; Kunos, G.; et al. Chronic Alcohol Produces Neuroadaptations to Prime Dorsal Striatal Learning. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 14783–14788. [[CrossRef](#)]
148. Wolf, M.E.; Tseng, K.Y. Calcium-Permeable AMPA Receptors in the VTA and Nucleus Accumbens after Cocaine Exposure: When, How, and Why? *Front. Mol. Neurosci.* **2012**, *5*, 72. [[CrossRef](#)]
149. Lüscher, C.; Malenka, R.C. Drug-Evoked Synaptic Plasticity in Addiction: From Molecular Changes to Circuit Remodeling. *Neuron* **2011**, *69*, 650–663. [[CrossRef](#)]
150. Wolf, M.E. The Bermuda Triangle of Cocaine-Induced Neuroadaptations. *Trends Neurosci.* **2010**, *33*, 391–398. [[CrossRef](#)]
151. Gil, M.; Zhen, X.; Friedman, E. Prenatal Cocaine Exposure Alters Glycogen Synthase Kinase-3beta (GSK3beta) Pathway in Select Rabbit Brain Areas. *Neurosci. Lett.* **2003**, *349*, 143–146. [[CrossRef](#)]
152. Svenningsson, P.; Tzavara, E.T.; Carruthers, R.; Rachleff, I.; Wattler, S.; Nehls, M.; McKinzie, D.L.; Fienberg, A.A.; Nomikos, G.G.; Greengard, P. Diverse Psychotomimetics Act through a Common Signaling Pathway. *Science* **2003**, *302*, 1412–1415. [[CrossRef](#)] [[PubMed](#)]
153. Nwaneshiudu, C.A.; Unterwald, E.M. NK-3 Receptor Antagonism Prevents Behavioral Sensitization to Cocaine: A Role of Glycogen Synthase Kinase-3 in the Nucleus Accumbens. *J. Neurochem.* **2010**, *115*, 635–642. [[CrossRef](#)] [[PubMed](#)]
154. Shi, X.; McGinty, J.F. Repeated Amphetamine Treatment Increases Phosphorylation of Extracellular Signal-Regulated Kinase, Protein Kinase B, and Cyclase Response Element-Binding Protein in the Rat Striatum. *J. Neurochem.* **2007**, *103*, 706–713. [[CrossRef](#)] [[PubMed](#)]
155. Miller, J.S.; Tallarida, R.J.; Unterwald, E.M. Cocaine-Induced Hyperactivity and Sensitization Are Dependent on GSK3. *Neuropharmacology* **2009**, *56*, 1116–1123. [[CrossRef](#)]
156. Miller, J.S.; Barr, J.L.; Harper, L.J.; Poole, R.L.; Gould, T.J.; Unterwald, E.M. The GSK3 Signaling Pathway Is Activated by Cocaine and Is Critical for Cocaine Conditioned Reward in Mice. *PLoS ONE* **2014**, *9*, e88026. [[CrossRef](#)]
157. Shi, X.; McGinty, J.F. D1 and D2 Dopamine Receptors Differentially Mediate the Activation of Phosphoproteins in the Striatum of Amphetamine-Sensitized Rats. *Psychopharmacology* **2011**, *214*, 653–663. [[CrossRef](#)]
158. Xu, C.M.; Wang, J.; Wu, P.; Xue, Y.X.; Zhu, W.L.; Li, Q.Q.; Zhai, H.F.; Shi, J.; Lu, L. Glycogen Synthase Kinase 3 $\beta$  in the Nucleus Accumbens Core Is Critical for Methamphetamine-Induced Behavioral Sensitization. *J. Neurochem.* **2011**, *118*, 126–139. [[CrossRef](#)]
159. Xing, B.; Liang, X.P.; Liu, P.; Zhao, Y.; Chu, Z.; Dang, Y.H. Valproate Inhibits Methamphetamine Induced Hyperactivity via Glycogen Synthase Kinase 3 $\beta$  Signaling in the Nucleus Accumbens Core. *PLoS ONE* **2015**, *10*, e0128068. [[CrossRef](#)]
160. Wang, J.; Sun, L.L.; Zhu, W.L.; Sun, Y.; Liu, J.F.; Lu, L.; Shi, J. Role of Calcineurin in the VTA in Rats Behaviorally Sensitized to Methamphetamine. *Psychopharmacology* **2012**, *220*, 117–128. [[CrossRef](#)]
161. Park, H.J.; Cui, F.J.; Hwang, J.Y.; Kang, U.G. Effects of Clozapine on Behavioral Sensitization Induced by Cocaine. *Psychiatry Res.* **2010**, *175*, 165–170. [[CrossRef](#)]
162. Perrine, S.A.; Miller, J.S.; Unterwald, E.M. Cocaine Regulates Protein Kinase B and Glycogen Synthase Kinase-3 Activity in Selective Regions of Rat Brain. *J. Neurochem.* **2008**, *107*, 570–577. [[CrossRef](#)]
163. Yang, G.; Liu, L.; Zhang, R.; Li, J.; Leung, C.K.; Huang, J.; Li, Y.; Shen, B.; Zeng, X.; Zhang, D. Cannabidiol Attenuates Methamphetamine-Induced Conditioned Place Preference via the Sigma1R/AKT/GSK-3 $\beta$ /CREB Signaling Pathway in Rats. *Toxicol. Res.* **2020**, *9*, 202–211. [[CrossRef](#)]
164. Kalivas, P.W.; Stewart, J. Dopamine Transmission in the Initiation and Expression of Drug- and Stress-Induced Sensitization of Motor Activity. *Brain Res. Rev.* **1991**, *16*, 223–244. [[CrossRef](#)]
165. Hyman, S.E. Addiction to Cocaine and Amphetamine. *Neuron* **1996**, *16*, 901–904. [[CrossRef](#)]
166. Enman, N.M.; Unterwald, E.M. Inhibition of GSK3 Attenuates Amphetamine-Induced Hyperactivity and Sensitization in the Mouse. *Behav. Brain Res.* **2012**, *231*, 217–225. [[CrossRef](#)]
167. Kim, W.Y.; Jang, J.K.; Lee, J.W.; Jang, H.; Kim, J.H. Decrease of GSK3 $\beta$  Phosphorylation in the Rat Nucleus Accumbens Core Enhances Cocaine-Induced Hyperlocomotor Activity. *J. Neurochem.* **2013**, *125*, 642–648. [[CrossRef](#)]
168. Shi, X.; Miller, J.S.; Harper, L.J.; Poole, R.L.; Gould, T.J.; Unterwald, E.M. Reactivation of Cocaine Reward Memory Engages the Akt/GSK3/MTOR Signaling Pathway and Can Be Disrupted by GSK3 Inhibition. *Psychopharmacology* **2014**, *231*, 3109–3118. [[CrossRef](#)]
169. Bowers, M.S.; Chen, B.T.; Chou, J.K.; Osborne, M.P.H.; Gass, J.T.; See, R.E.; Bonci, A.; Janak, P.H.; Olive, M.F. Acamprosate Attenuates Cocaine- and Cue-Induced Reinstatement of Cocaine-Seeking Behavior in Rats. *Psychopharmacology* **2007**, *195*, 397–406. [[CrossRef](#)]
170. Liddle, S.; Itzhak, Y. Variations in the Stimulus Salience of Cocaine Reward Influences Drug-Associated Contextual Memory. *Addict. Biol.* **2016**, *21*, 242–254. [[CrossRef](#)]
171. Alaghband, Y.; Marshall, J.F. Common Influences of Non-Competitive NMDA Receptor Antagonists on the Consolidation and Reconsolidation of Cocaine-Cue Memory. *Psychopharmacology* **2013**, *226*, 707–719. [[CrossRef](#)]
172. Itzhak, Y. Role of the NMDA Receptor and Nitric Oxide in Memory Reconsolidation of Cocaine-Induced Conditioned Place Preference in Mice. *Ann. N. Y. Acad. Sci.* **2008**, *1139*, 350–357. [[CrossRef](#)]
173. Shi, X.; von Weltin, E.; Barr, J.L.; Unterwald, E.M. Activation of GSK3 $\beta$  Induced by Recall of Cocaine Reward Memories Is Dependent on GluN2A/B NMDA Receptor Signaling. *J. Neurochem.* **2019**, *151*, 91–102. [[CrossRef](#)]

174. Prickaerts, J.; Moechars, D.; Cryns, K.; Lenaerts, I.; van Craenendonck, H.; Goris, I.; Daneels, G.; Bouwknecht, J.A.; Steckler, T. Transgenic Mice Overexpressing Glycogen Synthase Kinase 3beta: A Putative Model of Hyperactivity and Mania. *J. Neurosci.* **2006**, *26*, 9022–9029. [[CrossRef](#)]
175. German, P.W.; Fields, H.L. Rat Nucleus Accumbens Neurons Persistently Encode Locations Associated with Morphine Reward. *J. Neuro-Physiol.* **2007**, *97*, 2094–2106. [[CrossRef](#)]
176. Mazei-Robison, M.S.; Appasani, R.; Edwards, S.; Wee, S.; Taylor, S.R.; Picciotto, M.R.; Koob, G.F.; Nestler, E.J. Self-Administration of Ethanol, Cocaine, or Nicotine Does Not Decrease the Soma Size of Ventral Tegmental Area Dopamine Neurons. *PLoS ONE* **2014**, *9*, e95962. [[CrossRef](#)]
177. Neasta, J.; ben Hamida, S.; Yowell, Q.V.; Carnicella, S.; Ron, D. AKT Signaling Pathway in the Nucleus Accumbens Mediates Excessive Alcohol Drinking Behaviors. *Biol. Psychiatry* **2011**, *70*, 575–582. [[CrossRef](#)]
178. Qiao, X.; Gai, H.; Su, R.; Deji, C.; Cui, J.; Lai, J.; Zhu, Y. PI3K-AKT-GSK3 $\beta$ -CREB Signaling Pathway Regulates Anxiety-like Behavior in Rats Following Alcohol Withdrawal. *J. Affect. Disord.* **2018**, *235*, 96–104. [[CrossRef](#)]
179. Acquaaah-Mensah, G.K.; Kehrer, J.P.; Leslie, S.W. In Utero Ethanol Suppresses Cerebellar Activator Protein-1 and Nuclear Factor-Kappa B Transcriptional Activation in a Rat Fetal Alcohol Syndrome Model. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 277–283. [[CrossRef](#)]
180. De la Monte, S.M.; Wands, J.R. Chronic Gestational Exposure to Ethanol Impairs Insulin-Stimulated Survival and Mitochondrial Function in Cerebellar Neurons. *Cell. Mol. Life Sci.* **2002**, *59*, 882–893. [[CrossRef](#)]
181. Duverne, S.; Koechlin, E. Rewards and Cognitive Control in the Human Prefrontal Cortex. *Cereb. Cortex* **2017**, *27*, 5024–5039. [[CrossRef](#)]
182. Stefani, M.R.; Moghaddam, B. Rule Learning and Reward Contingency Are Associated with Dissociable Patterns of Dopamine Activation in the Rat Prefrontal Cortex, Nucleus Accumbens, and Dorsal Striatum. *J. Neurosci.* **2006**, *26*, 8810–8818. [[CrossRef](#)] [[PubMed](#)]
183. Shah, A.A.; Treit, D. Excitotoxic Lesions of the Medial Prefrontal Cortex Attenuate Fear Responses in the Elevated-plus Maze, Social Interaction and Shock Probe Burying Tests. *Brain Res.* **2003**, *969*, 183–194. [[CrossRef](#)]
184. Klenowski, P.M. Emerging Role for the Medial Prefrontal Cortex in Alcohol-Seeking Behaviors. *Addict. Behav.* **2018**, *77*, 102–106. [[CrossRef](#)] [[PubMed](#)]
185. Morgan, M.A.; LeDoux, J.E. Differential Contribution of Dorsal and Ventral Medial Prefrontal Cortex to the Acquisition and Extinction of Conditioned Fear in Rats. *Behav. Neurosci.* **1995**, *109*, 681–688. [[CrossRef](#)]
186. Quirk, G.J.; Beer, J.S. Prefrontal Involvement in the Regulation of Emotion: Convergence of Rat and Human Studies. *Curr. Opin. Neurobiol.* **2006**, *16*, 723–727. [[CrossRef](#)]
187. Malizia, A.L. What Do Brain Imaging Studies Tell Us about Anxiety Disorders? *J. Psychopharmacol.* **1999**, *13*, 372–378. [[CrossRef](#)]
188. Luo, J. GSK3beta in Ethanol Neurotoxicity. *Mol. Neurobiol.* **2009**, *40*, 108–121. [[CrossRef](#)]
189. Logrip, M.L.; Barak, S.; Warnault, V.; Ron, D. Corticostriatal BDNF and Alcohol Addiction. *Brain Res.* **2015**, *1628*, 60–67. [[CrossRef](#)]
190. Van der Vaart, A.; Meng, X.; Bowers, M.S.; Batman, A.M.; Aliev, F.; Farris, S.P.; Hill, J.S.; Green, T.A.; Dick, D.; Wolstenholme, J.T.; et al. Glycogen Synthase Kinase 3 Beta Regulates Ethanol Consumption and Is a Risk Factor for Alcohol Dependence. *Neuropsychopharmacology* **2018**, *43*, 2521–2531. [[CrossRef](#)]
191. Cheng, Y.; Huang, C.C.Y.; Ma, T.; Wei, X.; Wang, X.; Lu, J.; Wang, J. Distinct Synaptic Strengthening of the Striatal Direct and Indirect Pathways Drives Alcohol Consumption. *Biol. Psychiatry* **2017**, *81*, 918–929. [[CrossRef](#)]
192. Tsurutani, J.; Castillo, S.S.; Brognard, J.; Granville, C.A.; Zhang, C.; Gills, J.J.; Sayyah, J.; Dennis, P.A. Tobacco Components Stimulate Akt-Dependent Proliferation and NFkappaB-Dependent Survival in Lung Cancer Cells. *Carcinogenesis* **2005**, *26*, 1182–1195. [[CrossRef](#)]
193. Hudson, R.; Green, M.; Wright, D.J.; Renard, J.; Jobson, C.E.L.; Jung, T.; Rushlow, W.; Laviolette, S.R. Adolescent Nicotine Induces Depressive and Anxiogenic Effects through ERK 1-2 and Akt-GSK-3 Pathways and Neuronal Dysregulation in the Nucleus Accumbens. *Addict. Biol.* **2021**, *26*, e12891. [[CrossRef](#)]
194. Hermann, D.; Sartorius, A.; Welzel, H.; Walter, S.; Skopp, G.; Ende, G.; Mann, K. Dorsolateral Prefrontal Cortex N-Acetylaspartate/Total Creatine (NAA/TCr) Loss in Male Recreational Cannabis Users. *Biol. Psychiatry* **2007**, *61*, 1281–1289. [[CrossRef](#)]
195. Sarne, Y.; Mechoulam, R. Cannabinoids: Between Neuroprotection and Neurotoxicity. *CNS Neurol. Disord. Drug Targets* **2005**, *4*, 677–684. [[CrossRef](#)]
196. García-Arencibia, M.; González, S.; de Lago, E.; Ramos, J.A.; Mechoulam, R.; Fernández-Ruiz, J. Evaluation of the Neuroprotective Effect of Cannabinoids in a Rat Model of Parkinson's Disease: Importance of Antioxidant and Cannabinoid Receptor-Independent Properties. *Brain Res.* **2007**, *1134*, 162–170. [[CrossRef](#)]
197. Möller, T. Neuroinflammation in Huntington's Disease. *J. Neural Transm. Suppl.* **2010**, *117*, 1001–1008. [[CrossRef](#)]
198. Esposito, G.; de Filippis, D.; Maiuri, M.C.; de Stefano, D.; Carnuccio, R.; Iuvone, T. Cannabidiol Inhibits Inducible Nitric Oxide Synthase Protein Expression and Nitric Oxide Production in  $\beta$ -Amyloid Stimulated PC12 Neurons through P38 MAP Kinase and NF-KB Involvement. *Neurosci. Lett.* **2006**, *399*, 91–95. [[CrossRef](#)]
199. Esposito, G.; de Filippis, D.; Carnuccio, R.; Izzo, A.A.; Iuvone, T. The Marijuana Component Cannabidiol Inhibits  $\beta$ -Amyloid-Induced Tau Protein Hyperphosphorylation through Wnt/ $\beta$ -Catenin Pathway Rescue in PC12 Cells. *J. Mol. Med.* **2006**, *84*, 253–258. [[CrossRef](#)]

200. Molina-Holgado, F.; Pinteaux, E.; Heenan, L.; Moore, J.D.; Rothwell, N.J.; Gibson, R.M. Neuroprotective Effects of the Synthetic Cannabinoid HU-210 in Primary Cortical Neurons Are Mediated by Phosphatidylinositol 3-Kinase/AKT Signaling. *Mol. Cell. Neurosci.* **2005**, *28*, 189–194. [[CrossRef](#)]
201. Molina-Holgado, E.; Vela, J.M.; Arévalo-Martín, A.; Almazán, G.; Molina-Holgado, F.; Borrell, J.; Guaza, C. Cannabinoids Promote Oligodendrocyte Progenitor Survival: Involvement of Cannabinoid Receptors and Phosphatidylinositol-3 Kinase/Akt Signaling. *J. Neurosci.* **2002**, *22*, 9742–9753. [[CrossRef](#)]
202. Del Pulgar, T.G.; de Ceballos, M.L.; Guzmán, M.; Velasco, G. Cannabinoids Protect Astrocytes from Ceramide-Induced Apoptosis through the Phosphatidylinositol 3-Kinase/Protein Kinase B Pathway. *J. Biol. Chem.* **2002**, *277*, 36527–36533. [[CrossRef](#)]
203. Sánchez, M.G.; Ruiz-Llorente, L.; Sánchez, A.M.; Díaz-Laviada, I. Activation of Phosphoinositide 3-Kinase/PKB Pathway by CB(1) and CB(2) Cannabinoid Receptors Expressed in Prostate PC-3 Cells. Involvement in Raf-1 Stimulation and NGF Induction. *Cell. Signal.* **2003**, *15*, 851–859. [[CrossRef](#)]
204. Ozaita, A.; Puighermanal, E.; Maldonado, R. Regulation of PI3K/Akt/GSK-3 Pathway by Cannabinoids in the Brain. *J. Neurochem.* **2007**, *102*, 1105–1114. [[CrossRef](#)]
205. Valjent, E.; Pagès, C.; Hervé, D.; Girault, J.A.; Caboche, J. Addictive and Non-Addictive Drugs Induce Distinct and Specific Patterns of ERK Activation in Mouse Brain. *Eur. J. Neurosci.* **2004**, *19*, 1826–1836. [[CrossRef](#)]
206. Valjent, E.; Pagès, C.; Rogard, M.; Besson, M.J.; Maldonado, R.; Caboche, J. Delta 9-Tetrahydrocannabinol-Induced MAPK/ERK and Elk-1 Activation in Vivo Depends on Dopaminergic Transmission. *Eur. J. Neurosci.* **2001**, *14*, 342–352. [[CrossRef](#)]
207. Ackermann, T.F.; Kempe, D.S.; Lang, F.; Lang, U.E. Hyperactivity and Enhanced Curiosity of Mice Expressing PKB/SGK-Resistant Glycogen Synthase Kinase-3 (GSK-3). *Cell. Physiol. Biochem.* **2010**, *25*, 775–786. [[CrossRef](#)]
208. Rösner, S.; Leucht, S.; Lehert, P.; Soyka, M. Acamprosate Supports Abstinence, Naltrexone Prevents Excessive Drinking: Evidence from a Meta-Analysis with Unreported Outcomes. *J. Psychopharmacol.* **2008**, *22*, 11–23. [[CrossRef](#)]
209. Mason, B.J.; Goodman, A.M.; Dixon, R.M.; Hameed, M.H.A.; Hulot, T.; Wesnes, K.; Hunter, J.A.; Boyeson, M.G. A Pharmacokinetic and Pharmacodynamic Drug Interaction Study of Acamprosate and Naltrexone. *Neuropsychopharmacology* **2002**, *27*, 596–606. [[CrossRef](#)]
210. Allgaier, C.; Franke, H.; Sobottka, H.; Scheibler, P. Acamprosate Inhibits Ca<sup>2+</sup> Influx Mediated by NMDA Receptors and Voltage-Sensitive Ca<sup>2+</sup> Channels in Cultured Rat Mesencephalic Neurons. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 440–443. [[CrossRef](#)]
211. Littleton, J.M. Acamprosate in Alcohol Dependence: Implications of a Unique Mechanism of Action. *J. Addict. Med.* **2007**, *1*, 115–125. [[CrossRef](#)]
212. Skinner, M.D.; Lahmek, P.; Pham, H.; Aubin, H.J. Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. *PLoS ONE* **2014**, *9*, e87366. [[CrossRef](#)] [[PubMed](#)]
213. Gossop, M.; Carroll, K.M. Disulfiram, Cocaine, and Alcohol: Two Outcomes for the Price of One? *Alcohol. Alcohol.* **2006**, *41*, 119–120. [[CrossRef](#)] [[PubMed](#)]
214. Carroll, K.M.; Fenton, L.R.; Ball, S.A.; Nich, C.; Frankforter, T.L.; Shi, J.; Rounsaville, B.J. Efficacy of Disulfiram and Cognitive Behavior Therapy in Cocaine-Dependent Outpatients: A Randomized Placebo-Controlled Trial. *Arch. Gen. Psychiatry* **2004**, *61*, 264–272. [[CrossRef](#)] [[PubMed](#)]
215. Stoller, K.B.; Bigelow, G.E.; Walsh, S.L.; Strain, E.C. Effects of Buprenorphine/Naloxone in Opioid-Dependent Humans. *Psychopharmacology* **2001**, *154*, 230–242. [[CrossRef](#)]
216. Fudala, P.J.; Bridge, T.P.; Herbert, S.; Williford, W.O.; Chiang, C.N.; Jones, K.; Collins, J.; Raisch, D.; Casadonte, P.; Goldsmith, R.J.; et al. Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone. *N. Engl. J. Med.* **2003**, *349*, 949–958. [[CrossRef](#)]
217. Feng, B.; Obach, R.S.; Burstein, A.H.; Clark, D.J.; de Morais, S.M.; Faessel, H.M. Effect of Human Renal Cationic Transporter Inhibition on the Pharmacokinetics of Varenicline, a New Therapy for Smoking Cessation: An In Vitro–In Vivo Study. *Clin. Pharmacol. Ther.* **2008**, *83*, 567–576. [[CrossRef](#)]
218. Baker, T.B.; Piper, M.E.; Stein, J.H.; Smith, S.S.; Bolt, D.M.; Fraser, D.L.; Fiore, M.C. Effects of Nicotine Patch vs. Varenicline vs. Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA* **2016**, *315*, 371–379. [[CrossRef](#)]
219. Anthenelli, R.M.; Benowitz, N.L.; West, R.; St Aubin, L.; McRae, T.; Lawrence, D.; Ascher, J.; Russ, C.; Krishen, A.; Evins, A.E. Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers with and without Psychiatric Disorders (EAGLES): A Double-Blind, Randomised, Placebo-Controlled Clinical Trial. *Lancet* **2016**, *387*, 2507–2520. [[CrossRef](#)]
220. Benowitz, N.L.; Pipe, A.; West, R.; Hays, J.T.; Tonstad, S.; McRae, T.; Lawrence, D.; St Aubin, L.; Anthenelli, R.M. Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial. *JAMA Intern. Med.* **2018**, *178*, 622–631. [[CrossRef](#)]
221. Burns, J.C.; Heenan, K.; Letzkus, L.; Zanelli, S. Gabapentin for Pain, Movement Disorders, and Irritability in Neonates and Infants. *Dev. Med. Child* **2020**, *62*, 386–389. [[CrossRef](#)]
222. Anton, R.F.; Latham, P.; Voronin, K.; Book, S.; Hoffman, M.; Prisciandaro, J.; Bristol, E. Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients With Alcohol Withdrawal Symptoms: A Randomized Clinical Trial. *JAMA Intern. Med.* **2020**, *180*, 728–736. [[CrossRef](#)]

223. Hendrich, J.; van Minh, A.T.; Hebllich, F.; Nieto-Rostro, M.; Watschinger, K.; Striessnig, J.; Wratten, J.; Davies, A.; Dolphin, A.C. Pharmacological Disruption of Calcium Channel Trafficking by the A2 $\delta$  Ligand Gabapentin. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3628–3633. [[CrossRef](#)]
224. Sarhill, N.; Davis, M.P.; Walsh, D.; Nouneh, C. Methadone-Induced Myoclonus in Advanced Cancer. *Am. J. Hosp. Palliat. Care* **2001**, *18*, 51–53. [[CrossRef](#)]
225. Inturrisi, C.E.; Colburn, W.A.; Kaiko, R.F.; Houde, R.W.; Foley, K.M. Pharmacokinetics and Pharmacodynamics of Methadone in Patients with Chronic Pain. *Clin. Pharmacol. Ther.* **1987**, *41*, 392–401. [[CrossRef](#)]
226. Ferrari, A.; Coccia, C.P.R.; Bertolini, A.; Sternieri, E. Methadone–Metabolism, Pharmacokinetics and Interactions. *Pharmacol. Res.* **2004**, *50*, 551–559. [[CrossRef](#)]
227. Wang, X.; Zhang, R.; Wu, T.; Shi, Y.; Zhou, X.; Tang, D.; Yu, W.; So, E.C.; Wu, X.; Pan, Z.; et al. Successive Treatment with Naltrexone Induces Epithelial–Mesenchymal Transition and Facilitates the Malignant Biological Behaviors of Bladder Cancer Cells. *Acta Biochim. Biophys. Sin.* **2021**, *53*, 238–248. [[CrossRef](#)]
228. Romeo-Guitart, D.; Marcos-DeJuana, C.; Marmolejo-Martínez-Artesero, S.; Navarro, X.; Casas, C. Novel Neuroprotective Therapy with NeuroHeal by Autophagy Induction for Damaged Neonatal Motoneurons. *Theranostics* **2020**, *10*, 5154–5168. [[CrossRef](#)]
229. Zhao, Y.; Lin, Z.; Lin, Z.; Zhou, C.; Liu, G.; Lin, J.; Zhang, D.; Lin, D. Overexpression of Mucin 1 Suppresses the Therapeutical Efficacy of Disulfiram against Canine Mammary Tumor. *Animals* **2020**, *11*, 37. [[CrossRef](#)]
230. Zamek-Gliszczynski, M.J.; Mohutsky, M.A.; Rehmel, J.L.F.; Ke, A.B. Investigational Small-Molecule Drug Selectively Suppresses Constitutive CYP2B6 Activity at the Gene Transcription Level: Physiologically Based Pharmacokinetic Model Assessment of Clinical Drug Interaction Risk. *Drug Metab. Dispos.* **2014**, *42*, 1008–1015. [[CrossRef](#)]
231. Benowitz, N.L. Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 57–71. [[CrossRef](#)]
232. Lutfy, K.; Eitan, S.; Bryant, C.D.; Yang, Y.C.; Saliminejad, N.; Walwyn, W.; Kieffer, B.L.; Takeshima, H.; Carroll, F.I.; Maidment, N.T.; et al. Buprenorphine-Induced Antinociception Is Mediated by  $\mu$ -Opioid Receptors and Compromised by Concomitant Activation of Opioid Receptor-Like Receptors. *J. Neurosci.* **2003**, *23*, 10331–10337. [[CrossRef](#)] [[PubMed](#)]
233. Yan, B.C.; Wang, J.; Rui, Y.; Cao, J.; Xu, P.; Jiang, D.; Zhu, X.; Won, M.H.; Bo, P.; Su, P. Neuroprotective Effects of Gabapentin Against Cerebral Ischemia Reperfusion-Induced Neuronal Autophagic Injury via Regulation of the PI3K/Akt/MTOR Signaling Pathways. *J. Neuropathol. Exp. Neurol.* **2019**, *78*, 157–171. [[CrossRef](#)] [[PubMed](#)]
234. Nezamoleslami, S.; Sheibani, M.; Mumtaz, F.; Esmaeili, J.; Shafaroodi, H.; Dehpour, A.R. Lithium Reverses the Effect of Opioids on ENOS/Nitric Oxide Pathway in Human Umbilical Vein Endothelial Cells. *Mol. Biol. Rep.* **2020**, *47*, 6829–6840. [[CrossRef](#)] [[PubMed](#)]