Review

Mechanism of psychoactive substance-induced cognitive disorders: does tau protein play a role?

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Abstract

Psychoactive substances are a class of chemical substances which could cause public health threats. Cognitive disorders are a category of mental health disorders that primarily affect cognitive abilities. Tau protein could maintain neuronal cytoskeleton stabilization. Post-translational modification of tau, especially phosphorylation, is an important way to regulate the structure and function of tau and phosphorylated tau is closely related to cognitive function. Lots of studies have reported the phenomenon that psychoactive substances can cause cognitive function impairment. We reviewed recent related studies and discussed them by drug classification. We mainly focused on cognitive disorders caused by acute or chronic exposure of each drugs, animal experiments and the mechanisms associated with tau phosphorylation, then compared the similarities and differences among them, trying to find out the common rules. The results suggested that tau phosphorylation is involved in psychoactive substance-induced cognitive disorder and different psychoactive substances may act by affecting amount or activity of different kinases and phosphatases in the metabolic pathway of tau. We demonstrated that tau protein is a potential target for psychoactive substances induced cognitive disorder treatments.

Keywords: Psychoactive substances; Tau phosphorylation; Cognitive disorder

1. Introduction

Psychoactive drugs are substances that could change individuals' consciousness, mood or thinking processes. According to 2016 global quantities of drugs seized, traditional psychoactive substances can be classified into cannabis, cocaine, opioids, amphetamine-type stimulants (ATS) and others [1]. In recent years, designer drugs, a series of synthetic substances similar to the original drugs in structure or function, have emerged continuously, featured with avoiding being classified as illicit and/or spotted in standard drug tests [2]. Some of the designer drugs have been named as "New Psychoactive Substances (NPS)" by the European Union. In addition to synthetic NPS, the consumption of some natural plants, known as plants-based NPS, has been proved to have an impact on mental status, thus arousing social concerns. The use of NPS appeared to be rapidly emerging in some low- and middle-income countries. The limited capacity of forensic, law enforcement and health experts to identify different NPS and their use makes it challenging for countries to adequately address the threat of NPS [3]. The general classification and examples are shown in Table 1.

It was reported in a cross sectional study that the prevalence of cognitive disorders (CDs) was 21% for cannabis, 27% for stimulants and 38% for opioids with 123 cannabis users, 100 stimulants users and 26 opioids users included [4]. Also, CDs were identified in 34.6% of patients with chronic polysubstance use disorder in a prospective, longitudinal cohort study [5]. CDs are a category of mental health disorders that primarily affect cognitive abilities. The Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) defines six key domains of cognitive function: executive function, learning and memory, perceptual-motor function, language, complex attention, and social cognition. The increasing cases of CDs have become a major health problem with the aging of the population worldwide [6]. Considering that psychoactive drugs could induce CDs which would increase the burden on society, it is meaningful to discuss related mechanism and provide us with new idea for prevention and treatment methods. Cerebral hemorrhage or ischemia might partly explain some CDs identified in psychoactive substances users [7]. However, the clear mechanisms need to be thoroughly investigated.

Table 1. The classification of psychoactive substances.

Classification	Category	Example
Traditional psychoactive substances	Cannabis	Cannabis plants, Cannabis herb, Cannabis resin, Cannabis oil
	Coca/cocaine	Coca leaf, Cocaine hydrochloride, Cocaine base/paste, Other cocaine
	Opioids	Opium, Heroin, Morphine, Pharmaceutical opioids
	ATS	"Ecstasy", Methamphetamine, Amphetamine
	Others	Sedatives/Tranquillizers, Hallucinongens
NPS	Plant-based NPS	Khat, Kratom
	Synthetic NPS	Ketamine, Synthetic cannabinoids, Synthetic cathinones, Other NPS

Tauopathies are a group of neurodegenerative diseases closely related to CDs. Microtubule-associated protein tau is mainly expressed in neurons which maintains neuronal cytoskeleton stabilization. Post-translational modification of tau, especially phosphorylation, is an important way to regulate the structure and function of tau protein. Hyper-phosphorylated tau could be found in the brains of patients with Tauopathies such as Alzheimer's Disease (AD), progressive supranuclear palsy, and corticobasal degeneration [8,9]. For instance, AD, as a representative of Tauopathies, is featured by neuritic plaques (NPs) formed by beta-amyloid peptides(Abeta, Aβ) accumulation and neurofibrillary tangles (NFTs) formed by hyper-phosphorylated tau protein, and the latter may probably contribute to cognitive impairment [10,11]. Moreover, tau pathology may lead to CDs through grey matter loss [12]. Tau phosphorylation is mainly regulated by the dynamic balance of kinases and phosphatases activities [13–15]. Under some pathological conditions, the quantitative or qualitative upregulation of kinases or downregulation of phosphatases would lead to tau hyper-phosphorylation and may further cause accumulation of pathological tau, contributing to CDs. Researches on glycogen synthase kinase 3β (GSK-3β), Cyclin-dependent kinase-5 (CDK-5), protein phosphatase 2A (PP2A) and protein phosphatase 2B (PP2B) are the most in-depth. Psychoactive substances could induce tau hyper-phosphorylation through regulation of these kinases [16–18]. Hyper-phosphorylated tau may induce pathological changes through 4 types of mechanisms, which are, causing synaptic damage by affecting intracellular tau location, altering tau degradation and truncation process, enhancing tau aggregation and changing the relation between tau and its interaction substances [19]. The abnormal phosphorylated tau could lead to CDs [20]. Meaningfully, cerebral spinal fluid t-tau, p-tau [21,22] and plasma t-tau [22] could behave as biomarkers of AD which appears to be elevated in many cases of AD at all disease stages [21,22]. In other disease or states with CDs, CSF t-tau, p-tau and plasma t-tau may also be clinical parameters to provide basis for diagnosis. N-terminal fragment of tau levels even could predict future CDs and neurodegeneration [23].

In conclusion, tau phosphorylation is involved in the cognitive function impairment process and tau protein and p-tau could behave as biomarkers of Tauopathies. Based on these backgrounds, it is reasonable to speculate that tau could be a new diagnostic and therapeutic target for psychoactive substances-induced CDs. Thus, we selected 5 classes of representative drugs in psychoactive substances and reviewed related CDs and increasing of phosphorylation level of tau protein induced by them in detail and introduced other psychoactive substances-induced CDs briefly. We aim to explore the role of tau protein or tau phosphorylation in psychoactive substances-induced CDs.

Three independent reviewers separately conducted the literature search on two databases, PubMed and Google Scholar. Our search strategy contained three keywords: "psychoactive substances", "tau phosphorylation" and "cognitive disorders". Several synonyms were also included. The final literature search was performed on May 15th, 2021. We mainly searched relevant articles from the past 20 years which were published in English. Then duplicates within the retrieved articles were removed and divergences between the reviewers were discussed and resolved. In the initial search, studies were screened based on the content of title and abstract. After that, we obtained the full text of the retrieved studies and carefully read them to decide whether the full text meets with inclusion criteria or exclusion criteria. The inclusion criteria encompassed original works (including clinic studies and animal experiments) on the relationship between use of psychoactive substances and CDs in which tau phosphorylation plays a role. Studies that emphasizes other mechanisms unrelated to tau phosphorylation were excluded. And studies lacking a control group were also excluded.

2. Opioids

Opioids refer to natural medicines and semi-synthetic derivatives originating from opium which act on opioid receptors including μ, δ and κ [24]. Pain relief, including anesthesia, is the primary medical use of opioids. Opioids are often non-medically consumed for its strong effect of euphoria [25]. According to world drug report 2021, in 2019, an estimated 62 million people, or 1.2 per cent of the global population, used opioids at least once in 2019

[3]. Morphine, a representative opioid, consists of five condensed rings with a phenolic hydroxyl group at position 3, an alcohol hydroxyl group at position 6 and tertiary amine formed by the nitrogen (N) atom at position 17 which all exert important pharmacological roles [26]. For example, codeine is formed when morphine is O-methylated at position 3 the analgesia effect of which would reduce. Heroin is formed when morphine is O-acetylated at both position 3 and 6 which could pass through blood brain barrier more easily [24]. Opioids abuse took up 68 percent of all overdose deaths in 2017 [1]. In human researches, visual-spatial memory and working memory are damaged in heroin consumers and opioid-substituted patients [27,28]. Besides, impaired executive function and attention have been reported in heroin users and buprenorphine or methadone maintenance patients [27,29,30]. Moreover, acute use of morphine can cause transient anterograde and retrograde memory impairment in users [31].

Acute use of morphine has been shown to impair memory and learning function in different animal models. Memory impairment was detected by dark compartment test in male mice [32] and radial maze test in male Sprague-Dawley (SD) rats [33]. As to the investigation of chronic effects on cognitive functions, researchers have found that morphine could impair spatial learning and memory [34–37], especially short-term [35,36]. Meanwhile, object location memory could be impaired when tested by object-location memory task and elevated plus maze testing [38]. Besides, Wang *et al*. [39] implied that repeated morphine injection caused attention deficits and less cognition flexibility manifested by elevated omission and reduced accuracy. Surprisingly, voluntary exercise has been found to ameliorate the CDs that are induced by chronic morphine. Thus, voluntary exercise might be a potential method [37].

As for underlying mechanisms, opioid usage is associated with greater tau concentration in the brains of young opioids users [40]. The level of p-tau in any region of brain is significantly related to duration of opioids consumption. Analysis of hyper-phosphorylated tau in hippocampus, brainstem and basal ganglia indicated an excess of a pathogenic form of NFT (AT8-positive NFTs). Ramage *et al*. [41] reported that opiate could increase the deposition of hyper-phosphorylated tau at Thr231 and Ser202 sites in the hippocampus subiculum, entorhinal cortex, the neocortex, the locus coeruleus and the nucleus basalis of Meynert of young drug abusers when compared to those age-matched controls. Tau phosphorylated at Thr231 (AT180) is more widespread than at Ser202 (AT8) [41] as abnormal phosphorylation of tau is considered to start from C-terminal to N-terminal [42]. They further suggested that drug users show early AD-related brain pathology which is characterized by hyper-phosphorylated tau that may be the basis for CDs [43].

In rat embryo cortical neurons, morphine could induce increased phosphorylation of tau at tau1 (Ser199/Ser202), Ser396 and Ser404. Mitogen-activated protein kinases (MAPKs) may be a significant participator in AD neurodegeneration. c-Jun NH2-terminal kinases (JNK), members of MAPKs sub-group can upregulate phosphorylation of tau protein and deposition of amyloid protein. After morphine treatment, the level of phosphorylated JNK increased. In addition, the phosphorylation level of p38-MAPKs, another sub-group of MAPKs family, increased in a time-dependent manner after 10 μm morphine exposure, which further led to an increase of phosphorylated tau protein. However, the current study showed that SP600125, an inhibitor of JNK or SB203580, an inhibitor of p38 MAPK only significantly attenuated tau hyper-phosphorylation at Ser396 site while there was little change in the level of tau hyper-phosphorylated at tau-1 and Ser404 sites, which implied that JNK or p38-MAPK contributed to but were not the only determinant factor of tau phosphorylation [44]. Major kinases of tau (i.e., CDK5 and GSK-3β) were found upregulated in victims' and animals' use of opioids [43,45]. Moreover, downregulation of tau phosphatases also plays important role in increasing tau phosphorylation, such as PP1, PP2A and PP3. Opioids could upregulate PP1-specific endogenous inhibitors, which would not only lead to elevated phosphorylated tau, but also exacerbate damage of the brain from a repeated opioids exposure [46]. Besides, opiates could downregulate the activity of PP2A through demethylation, which would result in tau hyper-phosphorylation [47,48]. The corresponding possible mechanism diagram is shown in Fig. 1. Besides, researchers found that phosphorylated tau involved more anatomical region of the brain in heroin abusers compared to controls in which frontal cortex and fusiform gyrus are more sensitive to effect of heroin addiction. Tau protein in anatomical areas related to cognitive function might be easier to be phosphorylated. And age related tau phosphorylation is considered to be accelerated by heroin abuse [49].

According to world drug report, the global opium market is still expanding. At the same time, many studies have pointed out that opioids can lead to CDs in acute or chronic experiments. Studies of tau protein suggest that tau phosphorylation plays a critical role in CDs induced by opioids, with JNK/p38 MAPK involved in phosphorylation of tau upstream. Mechanism research can provide potential therapeutic targets for CDs caused by opioid abuse.

3. Amphetamine-type stimulants (ATS)

3.1 3,4-methylenedioxymethamphetamine (MDMA)

MDMA, a kind of amphetamine-type stimulants with methylenedioxy substitution on the phenyl ring, has both hallucinogenic and stimulant actions at relatively low doses [50]. Known as ecstasy, MDMA is often used in dance clubs due to its acute euphoric and hallucinogenic properties [51,52]. Nearly 20 million people globally are estimated to have used "ecstasy" in 2019 [3]. The quantities of "ecstasy" seized worldwide increased to 14 tons in 2016 [1].
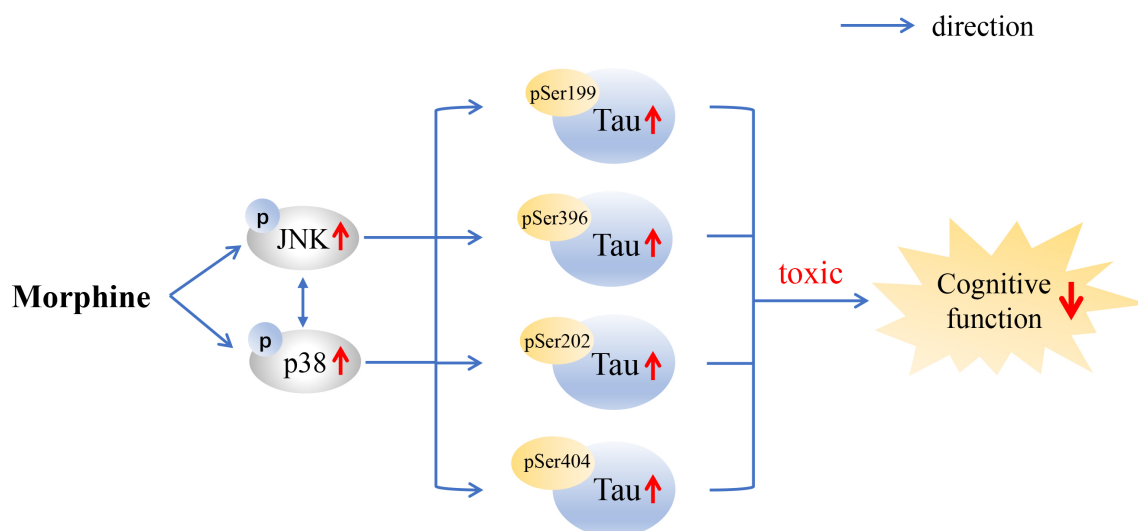
Fig. 1. Possible mechanism of morphine-induced-tau phosphorylation at different sites. Morphine treatment increase the phosphorylation level of JNK and p38, which in turn increase the expression of p-tau-Ser199, Ser202, Ser396 and Ser404, causing CDs. CDs, cognitive disorders; JNK, c-Jun NH2-terminal kinase.

Despite its neurotoxicity [51–54], there have also been studies testing the potential role of MDMA used in assisted psychotherapy of post-traumatic stress disorder (PTSD) [55]. In chronic users of MDMA, Wunderli *et al.* [56] found that heavy use of MDMA only is correlated with deficits in declarative memory, while additional dysfunction in working memory and executive functions appeared in poly-drug MDMA users. As for social cognition, they pointed out that people with long-term MDMA use might show an impairment in cognitive empathy capacity [57]. Furthermore, the CDs caused by dependence or abuse of MDMA could not be reversed by a 6-month prolonged abstinence [58]. In animal experiments, the results indicated that MDMA treatment leads to dose-dependent impairments of spatial learning and memory [59] and repeated treatment of MDMA impaired working memory and reduced cognitive flexibility [60]. Moreover, MDMA may exacerbate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced-CDs [61] and social stress plus MDMA enhanced the risk of developing CDs [62]. These results implied that exposure to MDMA may intensify the effects of other neurotoxic factors. However, physical exercise could decrease these harmful effects of MDMA, probably through decreased mitochondrial dysfunction [59].

In further studies, MDMA decreased mitochondrial trafficking in primary cultured neurons of hippocampus. This effect was correlated with CDs in a tau-related manner in which GSK-3β activity was influenced and phosphorylation level of tau increased, especially in Thr181 residue [63]. In a mouse model of AD, a study suggested that hippocampal accumulation of phosphorylated tau would lead to abnormal mitochondrial kinetics, changes of mitochondrial structure and function, and hippocampal based

learning and memory deficits [64]. Busceti *et al.* [65] pointed out that acute or repeated MDMA treatment could induce tau phosphorylation at Ser396 and Ser404 which was limited to the stratum radiatum of the CA2 area and the stratum lucidum and stratum radiatum of the CA3 area while there was no increase in the pyramidal cell layer of CA2 or CA3 area or other hippocampal regions. A dysfunction of CA3 neurons caused by tau phosphorylation might be responsible for CDs because the responsivity of the CA3–CA1 synapse seems to be correlated with associative learning [66]. As for the mechanisms of tau phosphorylation, GSK-3β and CDK-5 are two major enzymes involved in regulation of tau phosphorylation. GSK-3β activity is negatively regulated by the canonical wingless-type mouse mammary tumor virus (MMTV) integration site family (Wnt) pathway. After injection of MDMA, we found that Wnt pathway was inhibited, which followed the increase of Dickkopf-1(Dkk-1), and thus further led to an increase of GSK-3β activity. The level of Ser9-phosphorylated GSK-3β was also involved in the negative regulation of activity of GSK-3β. Besides, there was an increase in hippocampal levels of p35, p25, and CDK-5 in mice treated with MDMA. The corresponding possible mechanism diagram is shown in Fig. 2. However, there are conditions that learning deficit could be detected when tau hyper-phosphorylation could not be detected any more [65]. Thus, tau hyper-phosphorylation may be involved in, but is not the only decisive factor of MDMA-induced CDs. Besides, MDMA could increase the Ser199-phosphorylated tau protein independent of canonic pathway involving phosphorylated protein kinase B (AKT), CDK-5 and GSK-3β [67] which indicated that definite mechanism of MDMA-induced-tau phosphorylation needs further in-
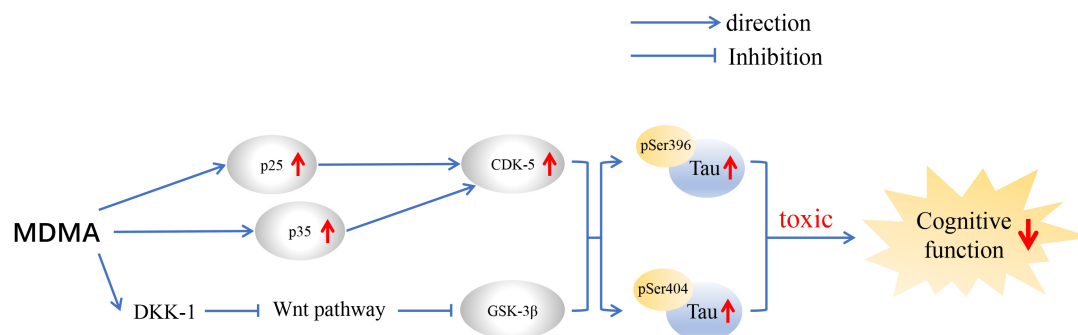
Fig. 2. Possible mechanism of MDMA-induced-tau phosphorylation at different sites. MDMA induced neurotoxicity through the increase of p35, p25 and CDK-5 levels and further lead to tau phosphorylation. Besides, MDMA treatment leads to increase of DKK-1, followed by inhibition of Wnt pathway and inhibition of GSK-3β activity. In conclusion, MDMA increases the level of CDK-5 and activates GSK3β, which in turn increase the expression of p-tau-Ser396 and Ser404, causing CDs. CDK-5, Cyclin-dependent kinase-5; CDs, cognitive disorders; MDMA, 3,4-methylenedioxymethamphetamine; Dkk-1, Dickkopf-1; GSK-3β, glycogen synthase kinase 3β; METH, Methamphetamine.

vestigation. Additionally, MDMA evoked an increase in tau phosphorylation (Ser396) in the hippocampus, striatum and cerebellum in the aged rats while there were no significant differences in adolescent group [68], which suggests a possible susceptibility to MDMA-related toxic events for the old.

3.2 Methamphetamine (METH)

METH, a kind of amphetamine type-stimulants derive from the β-phenylethylamine core structure [50], is widely abused for its stimulant, euphoric, empathogenic and hallucinogenic effects [69]. D-Methamphetamine, is a stronger psychostimulant, with 3–5 folds the central nervous system (CNS) activity when compared with L-methamphetamine. However, both enantiomers could affect dopamine release and induce stereotypy and psychosis at high doses [70]. Markets of METH are extending, which is one of the most worrying threats of drug use [1]. METH have not only neurotoxic [71] but also neuroprotective effects [72] when low doses of METH were administered within 12 h after severe traumatic brain injury (TBI) in rodents, which elucidates its therapeutic potential [73]. In chronic METH users, CDs occurred frequently as measured by Montreal Cognitive Assessment (MoCA) [74] especially in concentration and memory [75]. A meta-analysis revealed impairment in most cognitive domains [76]. 6–7-year old children with prenatal METH exposure scored significantly lower than controls on cognition in several domains [77]. Besides, a 12-week aerobic exercise may have beneficial effects on METH dependent patients with verbal learning and memory deficits [78]. In animal studies, chronic METH treatment could also impair cognitive functions [79–83], including deficits in reversal learning [79], disorders in alert exploratory behavior [80], impairments in recognition memory [81] and so on. In addition, Seyedhosseini *et al*. [82]

pointed out that repeated METH administration impaired only long-term recognition memory in somehow dose dependent manner while short-term remained unchanged.

As for further explorations on mechanism, researchers suggested that METH induced neurotoxicity probably by promoting abnormal tau phosphorylation in N2a cells [84], PC12 cells [85] or SH-SY5Y cells [86], where p-tau-Ser199, p-tau-Ser214 [84], p-tau-Ser396 [84,85] and p-tau-Thr205 [86] levels increased correspondingly. In addition, they found that the expression of p-GSK-3β-Tyr216 was elevated after METH exposure, which implies an activation of GSK-3β [84,85]. METH upregulated the expression of phosphorylated insulin receptor substrate-1 (IRS1) at Ser307 [84] and downregulated the expression of p-insulin receptor (IR) at Tyr1355 as well as p-IRS1 at Tyr896 [86], which implied an inhibition of insulin signal pathway. Besides, METH decreased the expression of AKT [18], another key insulin signal protein at Ser473 [84,86]. Thus, METH significantly decreased insulin signal and further induced downstream GSK-3β [84,86] and GSK-3α [86] activation and tau phosphorylation. In parallel, METH decreased the expression of phosphorylated extracellular regulated protein kinases (ERK) at Thr202 and Tyr204 which activated ERK and in turn induced tau phosphorylation [86]. Another similar experiment indicated that METH increased the p-Ser396-tau protein level in SH-SY5Y cells, primary cultured neurons and in mice brains. Furthermore, reducing α-syn level could relieve p-Ser396-tau overexpression and knocking out tau can effectively inhibit METH induced α-syn overexpression in mice brains [87] while another study from the same research group reported that tau phosphorylation might be indirectly promoted by excess α-syn through GSK3β and CDK5 [88] in which both tau phosphorylation and α-syn contributed to METH-induced neurotoxicity in mice brains, indicat-
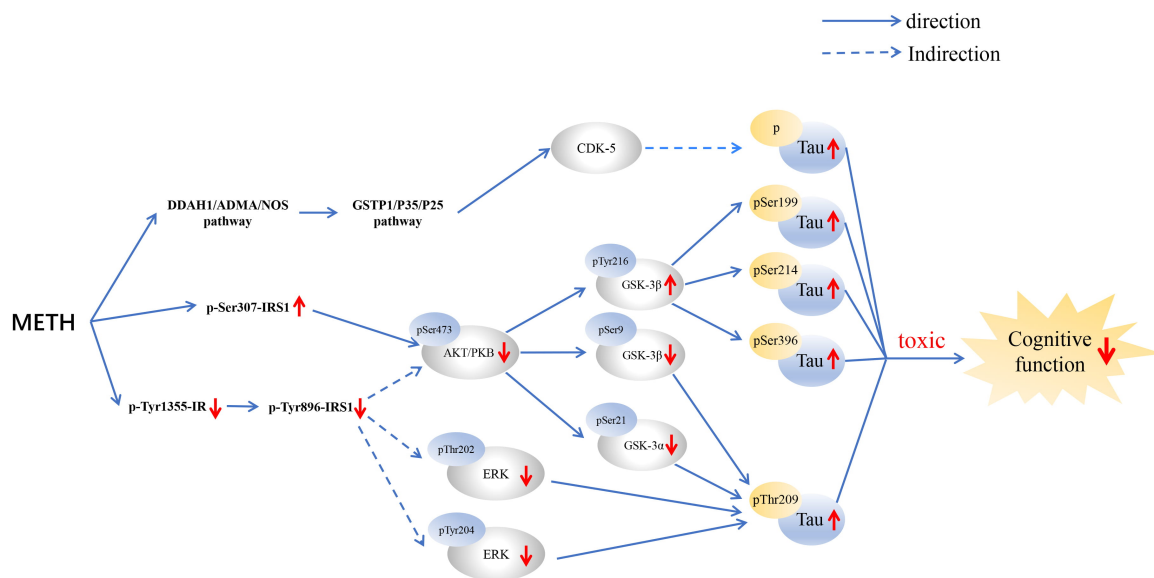
Fig. 3. Possible mechanism of METH-induced-tau phosphorylation at different sites. METH induced neurotoxicity through the activation of DDAH1/ADMA/NOS pathway, further resulting in activation of GSTP1/p35/p25/CDK-5 pathway which could further lead to tau phosphorylation. Besides, the insulin signal is transmitted through IR and IRS1. METH treatment leads to AKT phosphorylation (inhibition of insulin pathway). AKT phosphorylates GSK3β and GSK3α in different phosphorylation sites including Ser199, Ser214 and Ser396 (inhibition of kinase activity). In parallel, p-IRS1 actives MAPK/ERK cascade, both of the two pathways are participated in p-tau-Thr209 regulation. In conclusion, METH activates CDK-5, GSK3α/β and ERK, which in turn increase the expression of p-tau, causing CDs. AKT, protein kinase B; CDK-5, Cyclin-dependent kinase-5; DDAH1/ADMA/NOS, dimethylarginine dimethylaminohydrolase 1/asymmetric dimethylated L-arginine/Nitric Oxide Synthase; ERK, extracellular regulated protein kinases; GSTP1, glutathione S-transferase P1; IR, insulin receptor; IRS1, insulin receptor substrate-1; GSK-3β, glycogen synthase kinase 3β; MAPK, Mitogen-activated protein kinase.

ing an vicious circle between α-syn and tau in METH abusers. Xiao *et al.* [89] pointed out that METH exposure significantly upregulated the expression of phosphorylated tau at Ser396 and Thr231 sites in a dose- and time-dependent manner both *in vivo* (hippocampus of SD rats) and *in vitro* (SH-SY5Y cells). METH induced oxidative stress damage through the activation of dimethylarginine dimethylaminohydrolase 1/asymmetric dimethylated L-arginine/Nitric Oxide Synthase (DDAH1/ADMA/NOS) pathway, further resulting in activation of glutathione S-transferase P1 (GSTP1)/p35/p25/CDK-5 pathway [90]. The corresponding possible mechanism diagram is shown in Fig. 3. Besides, it has been reported that enhanced CDK-5 activity and translocation of p35 to membrane were detected in the ventral striatum of acute and chronic METH-treated rats [91].

In summary, ATS can cause various damages to the human body. Multiple studies have demonstrated its deleterious effects on the CNS, and the impairment is irreversible even after abstinence. At the same time, studies on tau protein suggest that we can delay the impairment progress by interfering tau phosphorylation which may involve changes in kinases, either GSK-3β or CDK-5, providing a further target upstream of the tau.

4. Cocaine

Cocaine, or benzoylmethylecgonine, is a kind of tropane alkaloid that is extracted from the leaves of the coca plant, which is ground into a paste and contains 70% pure cocaine [92,93]. It is usually treated with acid to form cocaine hydrochloride (HCl) salt which makes it water soluble and so can be absorbed through the nasal mucosa [93]. It is a strong stimulant mostly used as a recreational drug [94] which often acts as a CNS stimulant and as an appetite suppressant [95]. In the medical utility of cocaine, it can be used as a local numbing agent to help with painful procedures [96]. However, excessive and repeated cocaine consumption is also associated with an increased risk of a range of somatic, psychological and social problems, such as psychosis and aggression [97–99]. An estimated 20 million people used cocaine in 2019, corresponding to 0.4 per cent of the global population [3]. Because of its high addictive potential and harmful effects on mental and physical well-being [100,101], the use of cocaine is a major public health issue with substantial social and economic costs [100].

Up to now, studies on acute cocaine administration have suggested enhancement of response inhibition and psychomotor speed [102]. As for response inhibition, previous study indicated a dose–effect relationship of im-

paired response inhibition [103] and a significant increase in the number of responses per second after cocaine treatment [104]. Notably, it was concluded that interference of cocaine with cognitive impulse control and functional corticostriatal connectivity depends on the dopamine β-hydroxylase enzyme (DBH) genotype [106]. For another, long term effects of cocaine showed a wide array of deteriorated cognitive functions rather than with specific CDs [106]. When consumed over an extended period of time, cocaine was associated with deficits in attention, verbal learning/memory, and working memory constructs [107] and the group of patients with serious cocaine dependence may have difficulty in recovering from memory and attention deficits in short term [108]. Moreover, cocaine users performed worse in the Tic Tac Toe task, a spatial working memory task [109]. When it comes to the reversibility of long-term cocaine-induced disorders, users who ceased taking cocaine seemed to recover completely, which suggest that cognitive impairment might be reversible within 1 year [110]. But increased depression and anxiety are specifically related to more cognitive control breakdowns toward cocaine cues in veterans [111]. Cocaine has been shown, in animals, to acutely increase dopamine release in the mesocorticolimbic brain reward system, and conversely, to cause hypodopaminergic activity in the prefrontal cortex when administered chronically [112,113]. In other words, cocaine imposed different effects upon cognitive function according to different administration schedule and affect different brain regions. For instance, cocaine has been proved to improve the marmosets' recognition memory when given acutely post sample, whereas it had a detrimental effect after the repeated exposure [114]. Another related research found that cocaine-naïve monkeys performed better in stimulus discrimination and reversal task compared to monkeys who had previously self-administered cocaine [115].

As for the underlying mechanisms of cocaine-induced CDs and the role of tau plays in this process, certain achievements have been made. Researchers found that the levels of phosphorylated tau at Ser199/202 and Ser396/404 in paired helical filaments (PHFs), a critical component of neurofibrillary tangles in AD, were elevated in rat brain hippocampus, cortex, and caudate-putamen on day 8 and day 16 after the injection of cocaine compared with saline control rat at the same brain regions. Furthermore, although CDK5 is an immediate downstream target of cocaine-regulated transcription factor and cocaine injection could induce significant hyper-phosphorylation of tau, the overexpression of CDK5 and p35 was not detected, suggesting that hyper-phosphorylation of tau and neurofilament caused by cocaine may not correlate to CDK5 or p35. It is reasonable to speculate that cocaine might induce imbalance of multiple protein kinase and protein phosphatases, and further leading to hyper-phosphorylation of tau and neurofilament observed in the study [116]. Another related research used SH-SY5Y to examine the hypothesis that co-

caine may affect the metabolism of tau protein and would lead to changes in neurotransmitter uptake and release. The results implied that cocaine treatment caused no significant changes in total protein, however, it resulted in a reduction in tau protein in the cytoplasmic and membrane fractions, which proves that along with ultrastructural nuclear changes in the brains of cocaine abusers [117]. These contradictory outcomes indicated that the impact of cocaine on tau proteins may be paradoxical in different brain tissues. The action of cocaine on tau as well as other proteins, enzymes and neurotransmitters should be further explored in more comprehensive ways.

5. Ketamine

Ketamine, a derivative of phencyclidine (PCP), first aimed at lessening the serious psychodysleptic side effects and abuse potential of the parent drug [118] and provided as an anesthetic agent and analgesic drug in low doses [119–121]. The use of S-ketamine is increasing globally, because the S-enantiomer has been reported to be four folds more effective anesthetic and analgesic than the R-enantiomer and about two folds more potent than the racemic mixture of ketamine [121]. Many studies have demonstrated significant and rapid antidepressant effect of ketamine [122]. However, ketamine is still a drug with potent hallucinogenic property when repeatedly used over a sustained period, thus emerging as a kind of NPS and is abused worldwide, especially in East and South-East Asia [123,124]. In analgesic process, Kim et al. [125] found that patients with Complex Regional Pain Syndrome who received long-term frequent ketamine treatment showed CDs compared with those who did not. Besides, after initial sedation and administration of 0.3 mg/kg ketamine in elderly patients during ophthalmic surgery, the researchers detected changed cognitive status as measured by the short portable mental status questionnaire (SPMSQ), which is an immediate effect of ketamine [126]. Furthermore, several studies demonstrated that ketamine could induce CDs in healthy volunteers in acute experiment. Some results implied that ketamine impaired several domains of cognition [127]. Moreover, ketamine injection could impair verbal learning and recall [128]. As for chronic use of ketamine, worse verbal and visual memory performance [129] and other tests related with CDs were detected in chronic ketamine users [130]. Compared with METH, the ketamine-dependent patients impaired cognitive function more [131]. In addition, Liao Y et al. [132] demonstrated that abnormalities of white matter in bilateral frontal and left temporoparietal regions is correlated with prolonged ketamine use in dose-dependent manner which suggested a microstructural base for the alternations in cognition and experience in people with chronic ketamine use. In acute experiment of rodents, Nikiforuk A. et al. [133] suggested that ketamine impair cognition function of SD rats when assessed by attentional set-shifting task (ASST) and novel object recognition task (NORT). When ketamine

was administered to pregnant rats in the second trimester, CDs in offspring could be detected by Morris Water Maze (MWM) [134,135]. Furthermore, mice treated with ketamine in perinatal period showed dysfunction in a task of cognitive flexibility and abnormality in spontaneous alternation and deficits in NORT [136]. In chronic experiment of male C57BL/6 mice [137,138] or Institute of Cancer Research (ICR) mice [139,140], researchers found that ketamine intraperitoneal injection caused CDs when tested by Radial Arm Maze [137], MWM [137,139,140] or Y Maze [138].

When it comes to the underlying details of ketamine-induced CDs, by establishing a model of 6 months-ketamine administration in wild-type (C57BL/6) and Tau knockout mice, Li *et al.* [141] investigated the effects of different doses of ketamine administration on tau protein expression and phosphorylation in the mouse hippocampus and changes in α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor expression in the synaptic membrane. The results showed that long-term ketamine administration led to excessive tau protein phosphorylation at Ser202/Thr205 and Ser396 but not at Ser199, Ser262 and Ser404 [17] and that long term ketamine administration decreased AMPA receptor levels in the hippocampal cell membrane in a tau protein-dependent pattern, which revealed the role of tau protein phosphorylation in the mechanism of ketamine neurotoxicity [141]. The phosphorylation was mediated by increase in the activity of GSK-3β (at high doses) and CDK5 (long-term) and a decrease in the activity of PP2A [17]. However, another research reported that after 6 month-administration of ketamine there was a significant increase of hyper-phosphorylated tau at Ser199 in the layer I of prefrontal cortex of mice and in the outer layers of prefrontal cortex and deep layers of entorhinal cortical sections of monkeys. Moreover, this research also indicated that there might be a relationship between hyper-phosphorylation of tau and apoptosis. Therefore, the long-term ketamine toxicity might involve neurodegenerative process similar to that of aging or AD, which is another example of chronic experiment [142]. Besides, research showed that in acute experiment, levels of phosphorylated tau mRNA and hyper-phosphorylated tau at Ser404 significantly increased at 14 days after ketamine anesthesia in developing hippocampal tissue of neonatal rats [143]. In animal anesthesia, hyper-phosphorylation of tau at Ser396, Ser262, Thr181 and Ser202/Thr205 were observed 1 hour after ketamine/xylazine treatment in a dose-dependent manner in which ketamine/xylazine mixture is one of the most commonly used anesthetic agents in animal research and veterinary practice. Calmodulin-dependent protein kinase II (CaMKII) is the major upstream molecular event [144]. Considering all four experiment results, we could found that ketamine induced tau phosphorylation at different sites and different brain regions which may be caused by different doses and treatment time.

In recent years, postoperative cognitive dysfunction aroused increasing attention, when ketamine is used as an anesthetic, and we can reduce the dose or frequency to prevent CDs. In the condition that ketamine administration could induce CDs in offspring of pregnant rats or in mice treated in perinatal period, understanding the long-term damage of ketamine plays an important role, especially when some studies have indicated that CDs persists even after withdrawal.

6. Synthetic cannabinoids

Synthetic cannabinoids (SCs) first came out in the 1980s as laboratory research tools [145]. SCs have become popular recreational drugs among young adults in the USA [146]. They were usually advertised to contain only 'legal' and 'safe' compounds [147], leading to a misunderstanding of their harmfulness including adverse reactions, dependence, long-term effects and psychiatric consequences [148]. Mostly lipophilic and nonpolar, SCs generally consist of about 22 to 26 carbon atoms with a side chain of 4–9 saturated carbon atoms [149]. The structure makes them volatile when smoked and thus SCs were mainly consumed through smoking, inhalation and insufflation [150]. A model was proposed in order to summarize the chemical structures of the occurring SCs. The model structure consists of four key structural elements, namely "the core and substituents", "the link", "the ring and substituents" and "the tail" which signify altering positions. This method allowed the chemical structure of the SCs to be identified without the long chemical name [149].

SCs have been reported to represent more than half of the total NPS-related seizures in Europe in 2014 [151]. In the medical use, SCs are reported to be anti-inflammatory, antiemetic, analgesic, antineoplastic [152]. Acute psychotic reactions in healthy individuals could occur after a single or repeated use of SC, and may include a wide range of CDs [153]. In the research of Schwartz MD *et al.* [154], two outbreaks of agitated delirium were linked to the administration of the same previously unknown SCs. Moreover, SCs could exacerbate symptoms in patients already diagnosed with psychotic illness [155]. As to chronic effects, under the influence of long-term SCs, disturbance of fine motor skills, impairment of attention and concentration were found [156]. For another, SC users were found to have impairments in long-term memory and working memory, which was similar to recreational cannabis users [157]. Over the years, the effects of SCs have been investigated widely by performing an extensive range of tests in animal behavioral models [151]. Acute SC administration in rodents produced the cannabinoid tetrad of effects and dose-dependent anxiolytic and anxiogenic properties were found. Chronic SC administration produced CDs in rodents, especially exposed during adolescence [158]. Indeed, high doses of JWH-25 and JWH-073 induced convulsions, myoclonias and hyperreflexia in mice, which were

not usually observed after the administration of traditional cannabis [159].

When it comes to the underlying mechanisms of SCs-induced CD and the role phosphorylation of tau plays in this process, certain achievements have been made. Until now, two subtypes of cannabinoid Gi/o-coupled receptors, CB1 and CB2, have been totally found and identified. CB-1 receptors are found mainly in CNS, which could reduce cyclic adenosine monophosphate concentrations when stimulated. And CB-1 stimulation could cause hypothermia, analgesia, cataplexy, and locomotor suppression. Meanwhile, SCs also stimulate CB-2 receptors, which are mainly found in immune and hematopoietic cells [160]. Several findings indicated that the activation of both CB1 and CB2 receptors by natural or synthetic agonists, had certain beneficial effect by reducing the harmful tau phosphorylation, as well as by promoting the brain's intrinsic repair mechanisms [161]. For another, chronic treatment with arachidonyl-2-chloroethylamid (ACEA), a kind of CB1 selective agonist, reduced the levels of tau phosphorylated at Thr181 site in treated APP/PS1 mice [162]. As to the specific role for CB2 receptor in the modulation of tau phosphorylation, the administration of the CB2 receptor agonist JWH-133 has been proved to reduce phosphorylation of tau, thus reversing neurodegeneration, neuro-inflammation and spatial memory impairment in the okadaic acid (OKA)-induced AD model [163], along with another similar research shows that chronic JWH-133 administration reduced tau hyper-phosphorylation in APP/PS1 mice [164]. For the details, recent study showed that JWH133 reduced phosphorylation of tau and GSK3β activity in HEK293 tau cells, but the effects of JWH133 on phosphorylation of tau and GSK3β disappeared while blocking Adenosine Monophosphate Activated Protein Kinase (AMPK) activity, which indicated that the deletion of CB2R induced behavior damage and AD-like pathological alternation probably via AMPK/GSK3β pathway [165]. However, SCs have been reported to exhibit higher binding affinity at both CB1 and CB2 subtypes, and also to display varying intrinsic activity relative to Δ9-tetrahydrocannabinol (Δ9-THC) [166]. So the CDs caused by SCs may have a strong connection with the inhibition of NO-dependent tau hyper-phosphorylation. From the research of Giuseppe Esposito *et al.* [167], results demonstrated that SCs down-regulated inducible nitric oxide synthase (iNOS) protein expression and NO production in C6 cells and that WIN55, 212-2 inhibited tau protein hyper-phosphorylation in Aβ-stimulated PC12 cells.

In summary, despite the fact that the SCs has a great many research and clinical values with anti-inflammatory, antiemetic, analgesic, antineoplastic functions, it also goes hand in hand with many psychotic problems, especially a wide range of CDs. Contrary to most of the psychoactive substances we have discussed, the SCs play a role mainly through down-regulation of harmful tau phosphorylation rather than contributing to tau phosphorylation,

which suggests that SCs may pose neuroprotective properties and could have pharmacological and therapeutic potential. Nevertheless, considering the inherent danger that may accompany use of SCs, more detailed and profound researches need conducting before applying the mechanism to clinical practice.

7. Other psychoactive substances

Cannabis contained more than 550 chemical compounds, with more than 100 phytocannabinoids and aromatic terpenes being identified, including Δ9-THC and cannabidiol (CBD). These phytocannabinoids exert functions by binding to the cannabinoid receptors and other receptor systems [168]. It was estimated that roughly 200 million people used cannabis in 2019, representing 4 per cent of the global population. The number of cannabis users has increased by nearly 18 per cent over the past decade [3]. A meta-analysis showed that reduced cognitive functioning was associated with frequent or heavy cannabis use in adolescents and young adults [169], the underlying mechanism of which might be synaptic pruning and white matter development [170]. Moreover, there are gender differences in the impact on cognitive function [171]. Some of the effect of cannabis on cognition is similar to SCs due to similar active ingredients. Many research results suggested that high-dose cannabis or long-term use would cause CDs, while low-dose do not impair cognition and may even exert a protective or therapeutic effect [169,172–175].

Khat, a kind of plant-based NPS, is made from the leaves and shoots of an Arabian bush, which are chewed or made into tea and act as a stimulant [176,177]. Khat contains more than 40 compounds, including alkaloids, glycosides, tannins, flavonoids, terpenoids, amino acids, vitamins, and minerals. However, the main active ingredients are cathine and cathinone which are structurally related to amphetamine [178,179]. Several human studies [176] suggest that chronic khat use is associated with significant impairments in several cognitive domains, including inhibitory control [180], cognitive flexibility [181], working memory [181,182], behavioral control [183], learning [184], motor speed/coordination [184] and set-shifting/response inhibition [184]. Besides, research reported that only concurrent use of khat and tobacco would impair working memory [185], verbal learning and delayed recall deficits [186] while khat only users and nonusers were comparable [185,186] which are inconsistent with studies mentioned above. However, these results should arouse our attention in the CDs appeared in concurrent users. Several studies in animals also reported the CDs caused by khat in a dose and time dependent manner [176,187–189].

Kratom, leaves from tropical tree, causes stimulant and sedative effects in different doses. Raw leaves could be chewed directly or it could be swallowed as a pill, crushed and smoked and brewed as a tea [190]. Kratom
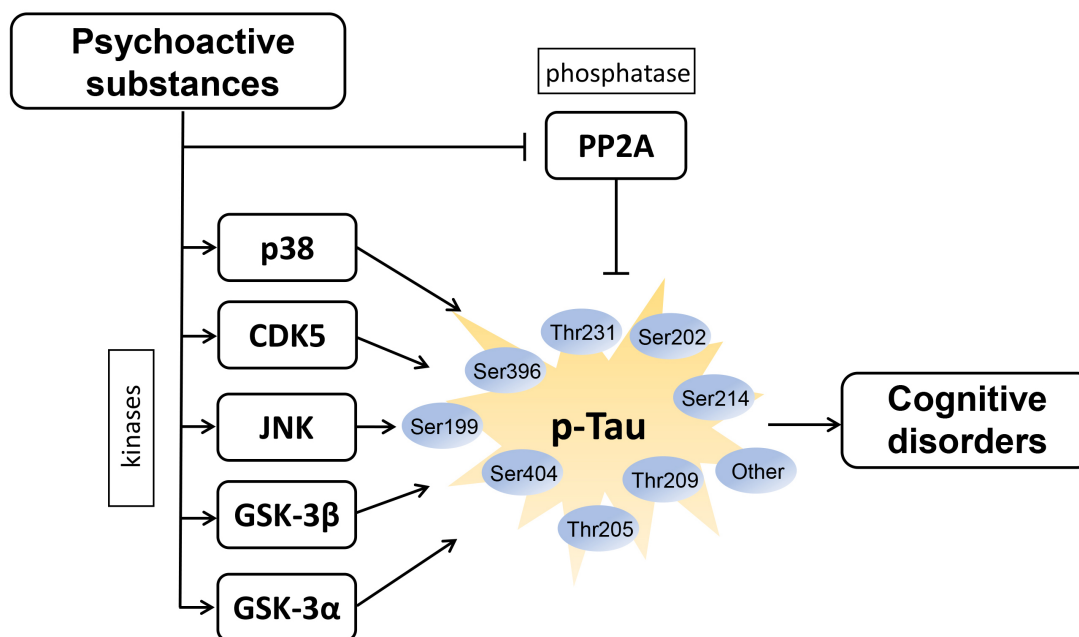
Fig. 4. Potential mechanism of psychoactive substances induced CDs. The overall mechanism could be summarized in "psychoactive substances-kinases/phosphatases-tau phosphorylation-CDs".

leaves contain over 25 alkaloids in which mitragynine and 7-hydroxymitragynine (7-HMG) are the primary active alkaloids in the plant. They are both indole-containing alkaloids. Mitragynine is suggested to 13 times more potent than morphine in regards to its opioid-like effects and 7-HMG is reported to be 4 times more powerful than mitragynine in its CNS stimulant effects [191]. In mice or rats, acute mitragynine independently led to impaired retrieval, memory consolidation and passive avoidance learning [192]. Chronic mitragynine administration impaired passive avoidance, object recognition learning [192], spatial learning [193], place learning, reversal learning [194] and memory [193,195].

Cathinone, naturally found in the Khat leaves, is a β-ketone amphetamine analogue and named (S)-2-amino-1-phenyl-1-propanone in organic chemistry nomenclature. Synthetic cathinones, including butylone, ethylone, mephedrone, methedrone, 3,4-methylenedioxypyrovalerone (MDPV) and methylone are all derived from methcathinone [196,197]. Mephedrone impaired working memory [198], verbal learning, verbal fluency, cognitive flexibility [199] and spatial memory [200] in users. Research show that adult rats would show impairments in spatial memory and reversal learning after repeated mephedrone exposure in adolescence and mephedrone would induce more deleterious effects on cognition than amphetamine due to GluN2B-containing N-methyl-D-aspartate (NMDA) receptor dominance [201] while exposure to mephedrone during gestation induced an impairment of spatial learning and reference memory in offspring [202]. MDPV impaired novel object recognition

function in a rat model of long-term voluntary binge-like self-administration [203]. Besides, MDPV caused widespread disruption of brain functional connectivity in rats which is linked to cognitive functions [204]. Several other studies in rodents also reported the CDs caused by synthetic cathinones [205–209].

8. Perspective

Overall, we demonstrated the potential role of tau protein in CDs induced by psychoactive substances. Abuse or inappropriate use of psychoactive substances could produce a variety of adverse reactions and social effects which highlights the importance of avoidance of drug abuse [2]. Cognitive function affects people's daily life, so it is of great significance to pay attention to the related mechanisms of CDs induced by psychoactive substances [6,210]. Many studies have shown that psychoactive substances can cause the phosphorylation of tau protein, and tau protein is closely associated with cognitive function. Both suggested that phosphorylated tau is involved in psychoactive substances-related CDs [211,212]. We summarized and proposed a potential mechanism of psychoactive substances induced CDs in Fig. 4. However, some experimental results, from the aspects of CDs and the sites of tau phosphorylation, show remarkable differences, which may be caused by different experimental environments, drug doses, treatment methods and time, and even individual differences. Moreover, the phosphorylation level of tau protein is regulated by the expression level or activity of related kinases, phosphatases, which makes related kinases and phosphatases the therapeutic targets on the pathway in turn [67,68]. Differ-

ent psychoactive substances may act by affecting amounts and activities of different kinases and phosphatases in the metabolic pathway of tau protein; different psychoactive substances may cause hyper-phosphorylation of different sites of tau protein, both of which are worthy of further investigation to elucidate the specific mechanisms [19,213]. All of the above provide us with a new idea for treatment in psychoactive substances induced CDs and the application, which would have broad social benefits and clinical significance. Fortunately, many new kinds of drugs targeting the prevention of tau aggregation and denaturation, with the purpose of treating CDs like AD, have been described in diverse studies with satisfactory results in recent years [214]. Nanotechnology also plays a promising role in tau-targeted pharmacotherapy because nanocarriers can improve the blood brain barrier (BBB) permeability of these new drugs [215].

In conclusion, psychoactive substances were primarily used in the clinical setting for therapeutic purposes. However, many people consume these compounds for different reasons, which may lead to CDs. Tauopathy is involved in psychoactive substance-induced CDs and different psychoactive substances may act by affecting the balance between kinases and/or phosphatases in the metabolic pathway of tau. However, the underlying mechanisms remain elusive in different conditions including different substances, different doses, different using terms or frequencies, different phosphorylation sites and different involved pathways. In the future, the specific role of tau in various psychoactive substances inducing CDs was warranted to be elucidated.

Abbreviations

ACEA, arachidonyl-2-chloroethylamid; AD, Alzheimer's Disease; AKT, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; AMPK, Adenosine Monophosphate Activated Protein Kinase; ASST, attentional set-shifting task; ATS, amphetamine-type stimulants; BBB, Blood Brain Barrier; CDK-5, Cyclin-dependent kinase-5; CDs, cognitive disorders; CNS, central nervous system; DBH, dopamine β-hydroxylase enzyme; DDAH1/ADMA/NOS, dimethylarginine dimethylaminohydrolase 1/asymmetric dimethylated L-arginine/Nitric Oxide Synthase; Dkk-1, Dickkopf-1; DSM-5, Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition; ERK, extracellular regulated protein kinases; GSK-3β, glycogen synthase kinase 3β; GSTP1, glutathione S-transferase P1; ICR, Institute of Cancer Research; iNOS, inducible nitric oxide synthase; IR, insulin receptor; IRS1, insulin receptor substrate-1; JNKs, c-Jun NH2-terminal kinases; MAPKs, Mitogen-activated protein kinases; MDMA, 3,4-methylenedioxymethamphetamine; METH, Methamphetamine; MoCA, Montreal Cognitive Assessment; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine;

MWM, Morris Water Maze; NFTs, neurofibrillary tangles; NORT, novel object recognition task; NPs, neuritic plaques; NPS, New Psychoactive Substances; PCP, phencyclidine; PHFs, paired helical filaments; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B; PTSD, post-traumatic stress disorder; SCs, Synthetic cannabinoids; SD, Sprague-Dawley; SPMSQ, short portable mental status questionnaire; TBI, traumatic brain injury; Wnt, wingless-type MMTV integration site family; Δ9-THC, Δ9-tetrahydrocannabinol.

Author contributions

XW developed the idea. YYW, JCL, JNH reviewed the articles and wrote the manuscript. GHW revised and modified the manuscript. All authors approved the final version for publication.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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