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REVIEW

Pharmacology and adverse effects of new psychoactive substances: synthetic cannabinoid receptor agonists

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Abstract Over the last decade, new psychoactive substances (NPS) have continuously been the focus of the international society since their emergence on the illicit drug market. NPS can be classified into six groups including; synthetic cannabinoid receptor agonists (SCRAs), stimulants, opioids, dissociatives, sedatives/hypnotics, and classic hallucinogens with psychoactive effects. These are sold as "herbal incense," "bath salts," "legal highs," and "research chemicals". They can be synthesized easily with slight changes in the chemical moieties of known psychoactive substances. NPS are sold worldwide via on- and off-line markets without proper scientific evaluation regarding their safety or harmfulness. Abuse of NPS poses a serious public health issue, and systematic studies on their adverse effects are lacking. Therefore, it would be meaningful to collect currently available data in order to understand NPS and to establish viable solutions to cope with the various health issues related to them. In this article, we reviewed the general pharmacological characteristics, recent findings, and adverse effects of representative NPS; SCRAs. SCRAs are known as the most commonly abused NPS. Most SCRAs, cannabinoid receptor 1 and cannabinoid receptor 2 agonists, are often associated with severe toxicities, including cardiotoxicity, immunotoxicity, and even death, unlike natural cannabinoid Δ^9-Tetrahydrocannabinol.

Keywords New psychoactive substances · Adverse effects · Synthetic cannabinoid receptor agonists · Pharmacology · Toxicity

Introduction

It is more than ten years since new psychoactive substances (NPS) emerged on the recreational drug market and have drawn public attention worldwide. The United Nations Office on Drugs and Crime (UNODC) defined NPS as "novel chemical substances with psychoactive properties, designed based on the chemical structure of a given parent drug and synthesized specifically for sale on the illicit market and to circumvent regulations on controlled substances" (UNODC 2017). The definition could be interpreted in two ways: first, that these substances have been detected, are available, and being used recently. Secondly, these substances are not classified in the international drug control statutes. In general, NPS are chemical analogs of already controlled substances, which are designed for similar effects on the central nervous system (CNS). Since these substances are synthesized with slight changes in existing psychoactive substances, they enter and exit the drug market extraordinarily fast in order to avoid regulations; as such this usually poses a struggle for the regulatory authorities (Evans-Brown and Sedefov 2017; Peacock et al. 2019a). NPS demand different administrative strategies from conventional controlled substances in order to not only monitor and regulate new compounds effectively but also to reduce their harmful effects (Peacock et al. 2019b).

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Governments find it difficult to regulate NPS because of the paucity of their pharmacological and toxicological information. Several behavioral, neurochemical, and electrophysiological studies have been carried out to help us understand the pharmacological mechanisms of action of NPS, but many of them have focused only on the acute toxicological consequences. Since they were recently made available, only a few epidemiological studies have been carried out to show the long-term effects of these compounds (Miliano et al. 2016). This could be the reason for the scarce data on the abuse liability or addictive properties of these substances. The increasing use of these compounds in young people is another aspect of concern. Adolescence, which is a critical developmental period, is commonly associated with an increase in drug abuse in the human population. As such, these group of people are particularly vulnerable to the effects of NPS (Johnston et al. 2003). According to previous studies, most brain receptor systems have been shown to mature slowly, reaching maximal levels around the age of 20. Thus, the use of NPS might influence neurodevelopment by inducing psychiatric disorders or other mental deficits (Paus 2005; Sussman et al. 2008).

There are several classifications of NPS. Some have divided NPS into six categories based on their chemical structures, they include: phenethylamines, piperazine, tryptamine, synthetic cathinones, SCRAs, and arylcyclohexylamines (Martinotti et al. 2015; Schifano et al. 2015). Another classification of these compounds is based on their pharmacological or toxicological effects: stimulants, entactogens, hallucinogens, and cannabis-like compounds (Miliano et al. 2016). Since substances under the same chemical structure category can exhibit individually different pharmacological effects, it is difficult to predict the pharmacological properties of substances based on their chemical structure. Therefore, it is important to gather information on the different health-related effects, despite the information from the user's report.

Among the NPS, SCRAs were found to be the most abused according to the results of surveys conducted by the European Monitoring Center for Drugs and Drug Addiction (EMCDDA 2015a, EMCDDA 2015b). SCRAs were introduced to the recreational markets in the early 2000s under various brand names such as; "Spice," "Herbal mixture," "Herbal blend" and so on. Their effects are similar to those of cannabis (Corazza et al. 2014; Hohmann et al. 2014; Khullar et al. 2014). A previous survey found that SCRAs were the second most popular recreational drugs after cannabis in the United States of America (USA), with a prevalence of 7.4–7.9% in people aged 15–18 years (Johnston et al. 2003).

In order to establish new and effective regulatory strategies, it is important to gather and analyze all types of scattered information on these NPS. Moreover, rationalizing and categorizing the scientific information and current legislative status would be helpful in understanding and dealing with the NPS phenomenon. In this regard, we presented the pharmacological properties and adverse effects of SCRAs, including recent regulatory measures, through an in-depth review of published literature.

SCRAs

History and trends

According to the UNODC, cannabis has been reported to be the most widely used drug, with 192.2 million past-year users worldwide in 2016 (UNODC 2018). Furthermore, over 13 million people aged 15–16 years have been reported to use cannabis in the past year (UNODC 2018). SCRAs with cannabis-like effects were first synthesized in the 1960s for cannabinoid research regarding the endocannabinoid system and its receptors inside and outside of the CNS. This was done in an attempt to develop pharmaceutical products with analgesic or anti-inflammatory properties without psychoactivity (Cooper 2016; Solimini et al. 2017). In the late 1970s, a researcher, John W. Huffman, created many SCRA analogs, which were called the JWH series. Despite their good intentions, many SCRAs with greater psychoactivity than natural cannabis were invented and became popular as recreational compounds, particularly among young people. The use of SCRAs was first reported in Europe in the early 2000s and the USA in 2008 (Cooper 2016). Several studies have shown that about 6–17% of college students in the USA have used SCRAs, and approximately 1% of European youths between the ages of 14 and 18 have used SCRAs at least once in their lifetime (Castaneto et al. 2014; Cooper 2016; Cohen and Weinstein 2018, NIDA 2020).

A total of 280 varieties SCRAs were reported by the UNODC by 2019 in 90 countries (UNODC 2020). SCRAs can be classified into 13 different types based on their chemical structures, according to a previous report (Solimini et al. 2017): benzoylindole, naphthoylindole, phenylacetylindole, indazolecarboxamide, cyclohexylphenyl, naphthylmethylindole, naphthyoylpyrrole, naphthylmethylindene, aminoalkylindole, adamantoylindole, tetramethylcyclopropylketoneindole, quinolinyl ester indole, and dibenzopyran (Table 1). Although the chemical structures of SCRAs differ from those of phytocannabinoids, their pharmacological properties are similar. They are marketed as herbal mixtures, sprayed on dried plants or herbs, and disguising them as a blend of natural products. The herbal components of the products can be obtained from common plants (Solimini et al. 2017). Since CP-47, 497, and JWH-018 were identified from the first generation of "Spice," a large number of various SCRAs appeared and dramatically increased in

Table 1 SCRA classes

Structural classification	Representative substances
Benzoylindoles	RCS-4, AM-694, AM-2233
Naphthoylindoles	JWH-018, JWH-073, JWH-210, JWH-081, JWH-122
Phenylacetylindoles	JWH-250, JWH-167, JWH-316
Indazolecarboxamides	AKB-48, MAB-CHMIACA, ADB-PINACA
Cyclohexylphenyls	CP-47497, CP-47497 homologs
Naphthylmethylindoles	JWH-175
Naphthylpyrroles	JWH-030, JWH-307, JWH-370
Naphthylmethylindenes	JWH-176, JWH-220
Aminoalkylindoles	WIN-55212–2
Adamantoylindoles	AB-001
Tetramethylcyclopropylketone indoles	UR-144, XLR-11
Quinolinyl ester indoles	QUPIC, 5F-QUPIC
Dibenzopyrans	HU-210

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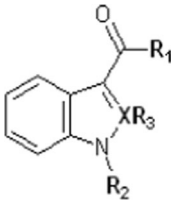
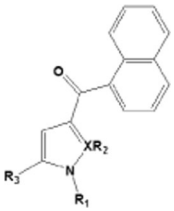
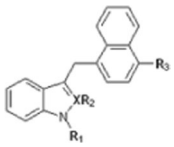
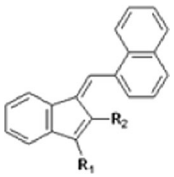
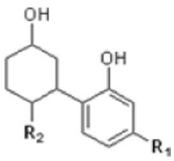
2014. (Auwarter et al. 2009; Uchiyama et al. 2009, UNODC 2018). SCRAs have numerous street names which include; Spice, K2, Yucatan Fire, Sense, Chill X Smoke, Genie, Blaze, Black Mamba, Paradise, Demon, Spike, Mr. Nice Guy, Green Buddha, Blonde, Summit, White Rabbit, and so forth (Solimini et al. 2017). Interestingly, the amounts and types of SCRAs vary even in products with the same brand name (Dresen et al. 2010).

SCRAs have continuously proliferated because they are synthesized easily through small alterations and can be an alternative to cannabis. Traditional legislative procedures could not keep pace with the dramatic popularity of SCRAs in the recreational drug market, which resulted in many countries adopting legal measures such as analog control and/or temporary scheduling systems to control these compounds more effectively. The USA, United Kingdom, Canada, Australia, Japan, and the Republic of Korea adopted an analog system to control SCRAs. Among them, the USA passed the Synthetic Drug Abuse Prevention Act in 2012, which banned certain types of SCRAs as Schedule I substances, followed by the Controlled Substances Act (USDEA 2012). The United Kingdom also controls SCRAs by classifying them based on their mother structures as Class B drugs under the Misuse of Drugs Act 1971. In the ROK, five types of SCRAs are controlled: naphthoylindoles, phenylacetylindole, cyclohexylphenyl, naphthoylpyrrole, and naphthylmethylindene. Other SCRAs with different mother structures are controlled individually as psychoactive substances or temporary controlled substances (Table 2).

Pharmacological properties

Δ^9-Tetrahydrocannabinol (THC), the main psychoactive substance of cannabis, has a high binding affinity for cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2) but acts as a partial agonist (Drummer et al. 2019). The inhibition constant (Ki) range of THC on the CB_1 and CB_2 receptors is 5 to 80 nM and 1.7 to 75 nM, respectively. The Ki value can differ depending on the conditions and source of the receptors (Drummer et al. 2019). Amongst the CB_1 and CB_2 receptors, CB_1 receptors are known to be responsible for the psychoactivity of THC, and both receptors exist in the pre-and post-synaptic neurons of the CNS (Maldonado et al. 2006; White 2017; Cohen and Weinstein 2018; Drummer et al. 2019). CB_1 receptors are G-protein-coupled and reduce cyclic adenosine monophosphate concentrations when stimulated (Maldonado et al. 2006; Mills et al. 2015; Huang et al. 2016; White 2017), indicating that they mediate the inhibition of neurotransmitter release (Huang et al. 2016). They are involved in various functions such as appetite, mood, sedation, spasticity, and analgesia (Drummer et al. 2019). According to a previous study using animals, stimulation of CB_1 exerted the classic tetrad of hypothermia, analgesia, cataplexy, and locomotor activity suppression (Mills et al. 2015). Since one of the purposes of inventing SCRAs was to get similar effects to THC, they are also able to bind to CB_1 and CB_2 receptors with varying affinities. Most SCRAs are potent and high-efficacy agonists. Interestingly, in contrast to THC, many SCRAs act as full agonists of CB_1 receptors (Solimini et al. 2017). The partial or full activation of CB_1 receptors and their binding affinities may correlate with the level of psychoactivity (Su et al. 2015). Unlike CB_1, CB_2 receptors were mostly identified in immune cells as well as in the CNS. The major function of CB_2 receptors is to inhibit the release of cytokines and migration of immune cells. Therefore, CB_2 receptor agonists can reduce inflammation-induced pain and have been expected to have inhibitory effects on tumor growth and peripheral antinociceptive properties (Wintermeyer et al. 2010). In addition, several studies have demonstrated that

Table 2 SCRA analogues controlled in Korea

Classification	Representative substances
JWH-018 and its analogs	 **R_1**: (hetero) aromatic ring, tetramethylcyclopropyl, adamanthyl, adamantylamine, (substituted) alkyl **R_2**: (substituted) alkyl **X**: carbon or nitrogen **R_3**: hydrogen or (substituted) alkyl
JWH-030 and its analogs	 **R_1**: (substituted) alkyl **X**: carbon or nitrogen **R_2, R_3**: hydrogen or (substituted) alkyl, aromatic compounds
JWH-175 and its analogs	 **R_1**: (substituted) alkyl **X**: carbon or nitrogen **R_2, R_3**: hydrogen or (substituted) alkyl, alkoxy
JWH-176 and its analogs	 **R_1**: (substituted) alkyl **R_2**: hydrogen or (substituted) alkyl
CP-47497 and its analogs	 **R_1**: (substituted) alkyl **R_2**: hydrogen or (substituted) alkyl

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CB_2 receptors that exist in the CNS are associated with the addiction to drugs such as cocaine, alcohol, and nicotine (Rajasekaran et al. 2013).

THC and SCRAs also acutely increase dopamine release and neuronal activity, but this increase is dramatically blunted when chronically exposed to the drugs (Bloomfield et al. 2016; Deng et al. 2018; Yeruva et al. 2019), suggesting the occurrence of tolerance. There is other evidence that CB_1 receptor agonists affect the dopaminergic system (Asaoka et al. 2016; Deng et al. 2018).

Phytocannabinoids are metabolized by cytochrome P450 (CYP450), the drug-metabolizing enzymes involved in the cellular detoxification of xenobiotics, cellular metabolism, and homeostasis (Solimini et al. 2017; Manikandan and Nagini 2018). CYP enzymes can be transcriptionally activated by various xenobiotics and endogenous substrates

through receptor-dependent mechanisms (Manikandan and Nagini 2018). The most well-known enzymes for metabolizing phytocannabinoids such as THC, cannabinol, and cannabidiol are CYP2C9, CYP2C19, and CYP3A4, respectively (Solimini et al. 2017). Although the metabolic pathways are relatively well elucidated for phytocannabinoids, only limited data about SCRAs was found. Multiple metabolites of SCRAs are expected to be produced by several metabolic pathways. The metabolism of SCRAs seems to involve both phases I and II processes. According to a previous report, SCRAs undergo hydroxylation and carboxylation in phase I and then conjugation with glucuronic acid in phase II (Chimalakonda et al. 2013; Zawilska and Wojcieszak 2014). The major metabolic pathway is mono-hydroxylation of the indole ring moiety in naphthoylindole, phenylacetylindole, and benzoylindole types (Zawilska and Wojcieszak 2014; Zendulka et al. 2016). Regarding the metabolic enzymes responsible for the mechanisms of synthetic cannabinoids, a recent finding suggested that the mother structures of SCRAs could inhibit CYP1A actively (Ashino et al. 2014). Other studies have shown that CYP2C9 and CYP1A2 are related to the metabolism of JWH-018 and AM-2201 (Chimalakonda et al. 2013), and CYP3A4 is responsible for the oxidation of AKB-48 (APINACA) (Holm et al. 2015; Zendulka et al. 2016). As phase II metabolic enzymes, JWH-018, JWH-073, UGT1A1, UGT1A9, and UGT2B7 were identified (Chimalakonda et al. 2011).

The remarkable difference between THC and SCRAs is that THC has only one metabolite, which is 11-OH-THC, with reduced CB_1 receptor affinity, via a phase I process mediated by CYP450 (Rajasekaran et al. 2013). In contrast, JWH-018 has been reported to have at least nine monohydroxylated metabolites, and some metabolites have been shown to retain significant binding affinity and activity at CB_1 receptors (Brents et al. 2011; Rajasekaran et al. 2013). Likewise, some metabolites of JWH-018 and JWH-073 also showed high affinity to CB_2 receptors (Rajasekaran et al. 2013).

Adverse effects

Cannabis is involved in numerous fatal and non-fatal intoxication cases. According to previous reports, cannabis has negative effects mostly on the cardiovascular system (Charles et al. 1979; Collins et al. 1985; Aryana and Williams 2007; Drummer et al. 2019). These intoxication cases were associated with chest pain, angina, arrhythmias, thrombus in the coronary artery, acute myocardial infarction, and minor strokes. THC itself has been known to adversely affect the cardiovascular system with manifestations such as: acute increase in heart rate, arrhythmias, coronary vasospasm, and acute myocardial infarction (Jones 2002; Sidney 2002; Aryana and Williams 2007; Goyal et al. 2017).

Other than these unfavorable effects on the cardiovascular system, cannabis has been reported to be responsible for poor fetal brain development, causing neurological impairments, hyperactivity, poor cognitive function, and changes in dopaminergic receptors in children, when exposed during pregnancy (Wang et al. 2004; Gunn et al. 2016; Brancato and Cannizzaro; 2018). Moreover, regular use of cannabis during pregnancy was associated with a significant decrease in birth weight (Fergusson et al. 2002; Gunn et al. 2016). Regarding fetal exposures, although the exact mechanisms are not elucidated yet, it is believed that in utero exposure with environmental factors can lead to persistent negative effects with increased susceptibility to certain diseases later in life (Dong et al. 2019).

The immune system can also be affected by exposure to THC. It is currently accepted that the immune system and inflammation play an important role in the etiology of neurological and psychiatric illnesses (Dong et al. 2019). Thus, THC might also cause neurological and psychiatric disorders via immunological pathways. Further studies elucidating the exact mechanisms of the relationship between the immune system and CNS are needed to confirm this hypothesis.

Regarding the adverse effects on the CNS, cannabis were reported to be responsible for drug dependency, psychosis, long-term changes in mental health, and impairment of psychomotor activity and cognitive performance (Asbridge et al. 2012; Karila et al. 2014; Busardo et al. 2017). In addition, many reports have suggested various functional and structural neuronal abnormalities with the regular use of cannabis (Batalla et al. 2013; Lorenzetti et al. 2016; Weinstein et al. 2016; Cohen and Weinstein 2018). According to these findings, cannabis cause structural changes in the gray matter and white matter in the limbic and prefrontal areas of the brain (Yucel et al. 2008; Batalla et al. 2013; Weinstein et al. 2016).

As previously mentioned, SCRAs have various pharmacological and metabolic features. SCRAs and their metabolites have potent affinity and activity at the CB receptors relative to cannabis. This makes it understandable why overdose of SCRAs can cause severe intoxication and possible death. Since SCRAs are popular recreational drugs, their major effects are related to the CNS. Several previous studies that incorporate the use of bioimaging techniques have shown that the volumes of the gray matter (Nurmedov et al. 2015) and white matter (Zorlu et al. 2016) in various regions of the brain were smaller in SCRA users. Similar to cannabis, SCRAs may induce reactions such as relaxation, euphoria, mood alteration, and cognitive impairment (Wilson et al. 2013). Because SCRAs can cause cognitive impairment, many people have been involved in road accidents, while under the influence of these substances (Cohen and Weinstein 2018). SCRAs can also induce several psychiatric disorders, including psychosis, anxiety, paranoia, and

hallucinations (Tait et al. 2016). The risks of these adverse effects tended to increase when SCRAs were used with other psychoactive substances (White 2017).

In terms of abuse liability of SCRAs, numerous reports have suggested psychological and/or physical dependence (Cha et al. 2014). Some synthetic compounds, such as JWH-018 and JWH-210, showed much stronger rewarding effects, which is one aspect of psychological dependence, than THC (Cha et al. 2014; 2015). Interestingly, putting together the previous findings on the psychological dependence of cannabinoids, they tended to induce rewarding effects rather than reinforcing effects, suggesting that they are less likely to draw cravings. However, the physical dependence of SCRAs varies from mild to severe, and its severity seems to be dependent on the dosage (Cooper 2016). Mild withdrawal symptoms include headache, severe anxiety, insomnia, nausea, vomiting, loss of appetite, and diaphoresis. Abrupt discontinuation of substances can cause severe symptoms such as reoccurring seizures and tachycardia, chest pain, palpitations, and dyspnea (Rodgman et al. 2014; Macfarlane and Christie 2015; Cooper 2016).

We further analyzed the gene–gene interactions in the nucleus accumbens of JWH-210-treated mice using an RT^2 Profiler™ Polymerase Chain Reaction Array Mouse Dopamine and Serotonin Pathway and web-based prediction tool (https://genemania.org) (Warde-Farley et al. 2010). We identified 23 genes that were highly associated with JWH-210 (Fig. 1). Among these genes, Slc6a4 (serotonin transporter),

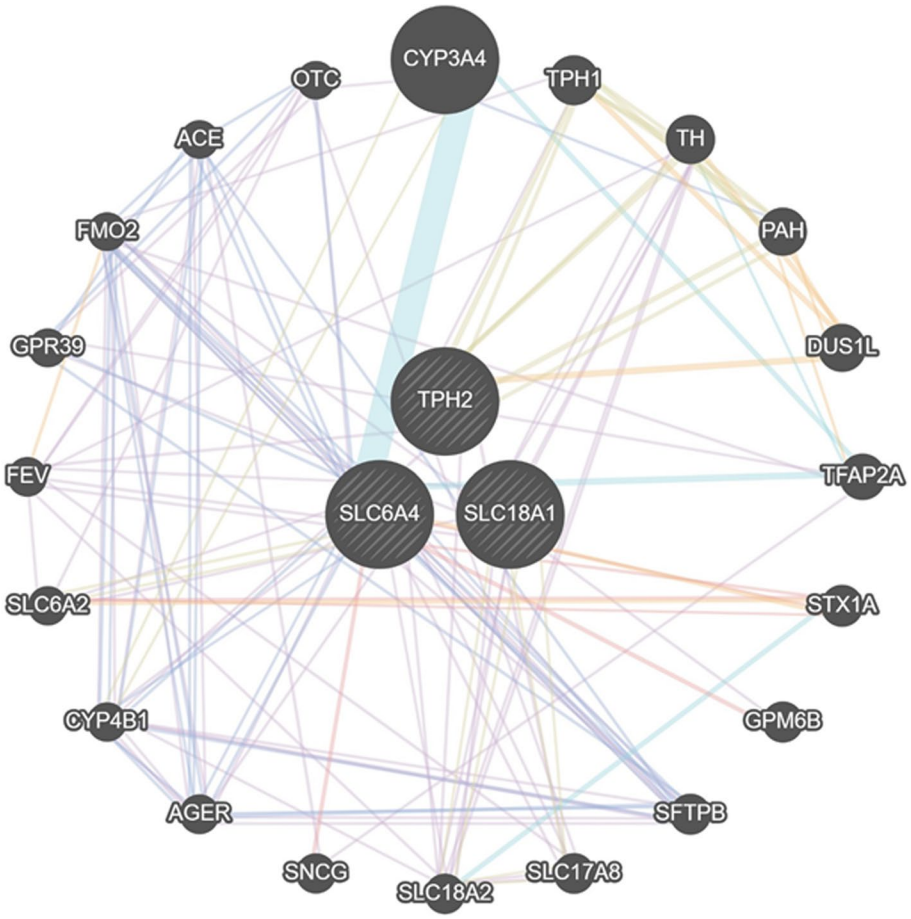

Fig. 1 Gene interaction network in the nucleus accumbens of JWH-210-treated (0.1 mg/kg per day, 5 days) mice. The gene–gene interaction network was generated by GeneMANIA. The color of lines represents the type of interaction in the network; physical interaction (pink), co-expression (purple), predicted (orange), co-localization (blue), and pathway (cyan). TPH2, tryptophan hydroxylase 2; SLC18A1, solute carrier family 18 member A; SLC6A4, solute carrier family 6 members 4; CYP3A4, cytochrome P450 family 3 subfamilies A member 4; TPH1, tryptophan hydroxylase 1; TH, tyrosine hydroxylase; PAH, phenylalanine hydroxylase; DUS1L, dihydrouridine synthase 1 like; TFAP2A, transcription factor AP-2 alpha; STX1A, syntaxin 1A; GPM6B, glycoprotein M6B; SFTPB, surfactant protein B; SLC17A8, solute carrier family 17 members 8; SLC18A2, solute carrier family 18 member A2; SNCG, synuclein gamma; AGER, advanced glycosylation end product-specific receptor; CYP4B1, cytochrome P450 family 4 subfamily B member 1; SLC6A2, solute carrier family 6 members 2; FEV, ETS transcription factor; GPR39, G protein-coupled receptor 39; FMO2, flavin-containing monooxygenase 2; ACE, angiotensin I converting enzyme; OTC, ornithine carbamoyltransferase

Slc18A1 (vesicular monoamine transporter 1), and Tph2 (tryptophan hydroxylase 2) were predicted as the genes mostly related to JWH-210. These gene–gene interactions may contribute to the regulation of SCRAs on the monoaminergic neuronal system of the brain reward circuit. We also observed that JWH-210 induced a dopamine release deficit in PC12 cells (unpublished data). In addition, JWH-081 and JWH-210 induced the distortion of nuclei and nucleus membranes in the core of the nucleus accumbens of mice, which were associated with a reduction in locomotor activity and rotarod retention time (Cha et al. 2015). Interestingly, chronic administration of JWH-210 induced a reduction in the gamma aminobutyric acid-ergic neuronal function in the striatum (unpublished data). This dysfunction may be associated with the regulation of the CB_1 receptor on GAD67 levels. These neurotransmission dysfunctions and neuronal cell damage may be associated with SCRA-induced neurotoxicity.

In contrast to cannabis, SCRAs have been found to be related to numerous death cases, according to previous reports. Several major causes of death were cardiovascular events (Mir et al. 2011; Davis and Boddington 2015), respiratory depression (Jinwala and Gupta 2012), pulmonary complications, and kidney injury (Bhanushali et al. 2013; Cohen and Weinstein, 2018). Among the lethal adverse effects, cardiovascular-related events were the most reported with various preclinical studies and clinical case reports. Several studies have shown that SCRAs may pose a risk for developing a cardiac arrhythmia (Hancox et al. 2020). We reported that JWH-030 induced QT prolongation in Sprague Dawley rats, which is associated with current channels and APD (Yun et al. 2016b). Furthermore, results showed that SCRAs reduced P21(RAC1) Activated Kinase I (PAK1) expression levels (Fig. 2) making it likely to be associated with a consequence of drug-induced cardiotoxicity (Yun et al. 2016a; Yoon et al. 2019a; 2019b; 2020a; 2020b).

We also showed that SCRAs suppressed the immune system (Yun et al. 2017) and reduced the weight of lymphoid organs (Gu et al. 2017) and T-cell/B-cell activator levels (Fig. 3). In addition, JWH-210 induced cytotoxicity in primary cultured splenocytes, which were attenuated by a CB_2 receptor antagonist.

Interestingly, some effects of SCRAs on gut microorganisms have been investigated by analyzing 16 s rRNA expression levels and calculating the proportion of gut microbiota in have effects on bacterial activity in the intestines (Appendino et al. 2008). The results showed that SCRAs changed the composition of gut microbiota with a decrease in domain bacteria such as *Lactobacillus acidophilus* and *Clostridium* clusters (Fig. 4). Interestingly, cannabinoids may regulate alcohol use disorders-induced behavioral phenotypes such as craving, impulsivity, and cognitive deficits via the regulation of microbiota–gut–brain axis (Karoly et al. 2020). Further research is required to clarify a possible role of microbiota-gut-brain axis in SCRA-induced CNS effects.

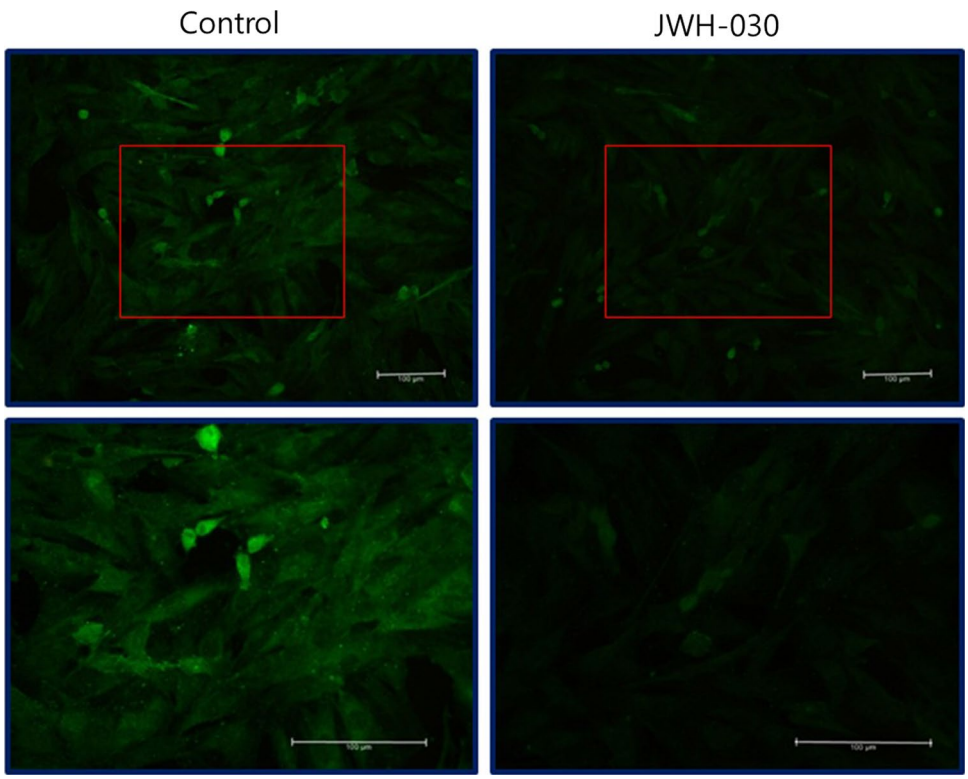

Fig. 2 Effects of JWH-030 on PAK1 protein expression levels in H9C2 cell. Lower pictures are enlarged images of upper pictures. PAK1 reduction is associated with cardiotoxicity. Scale bare: 100 μm

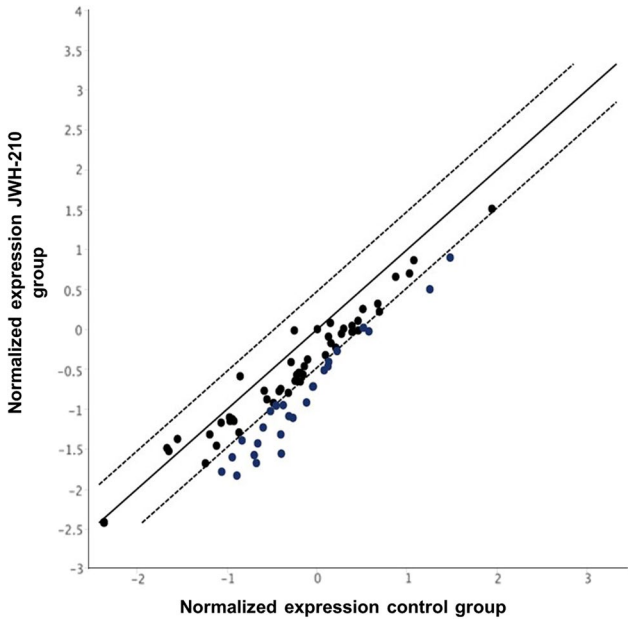

Fig. 3 T-cell and B-cell activators gene profiling results by using RT^2 Profiler™ Polymerase Chain Reaction Array Mouse T-Cell & B-Cell Activation (PAMM-053Z, QIAGEN). The threshold is 3-folds from the same normalized expression level. JWH-210 reduced immune cell activators

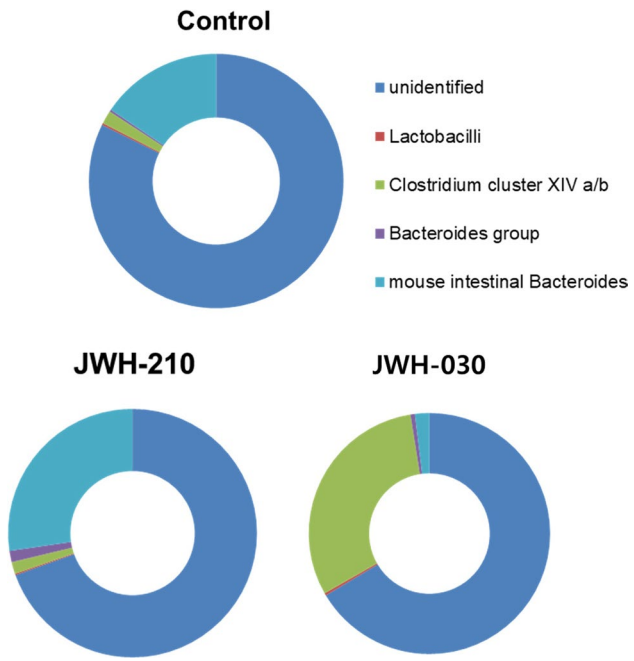

Fig. 4 The proportion of gut microbiota group based on 16S rRNA gene real-time polymerase chain reaction. Pie charts represent the mean frequencies for the main bacterial phyla in mice stool. Abundance was calculated using the phylum-specific 16S gene relative expression levels in relation to the amounts of the gene expression levels for the domain Bacteria set to 100%. The size of the circle refers to the relative frequency of gut microbiota in mice stool. JWHs induced gut microbiota disturbance

Several physiological complications other than the psychiatric effects caused by SCRAs have also been reported. Gastrointestinal problems are known to be one of the common adverse effects caused by SCRAs (Cooper 2016; White, 2017). Nausea and vomiting are the two major symptoms of gastrointestinal complications (Tait et al. 2016). A previous report suggested that these symptoms are similar to those of cannabis hyperemesis syndrome (White 2017). Hepatotoxicity and respiratory depression associated with the use of SCRAs have also been reported (Alon and Saint-Fleur 2017; Solimini et al. 2017). According to the report, rhabdomyolysis, liver dysfunction, and liver congestion were observed in SCRA users.

To summarize, the adverse effects of SCRAs are similar to those of cannabis in general, because they share the same receptors in the CNS. However, many SCRAs bind to CB_1 receptors with a much higher affinity than THC, indicating that they can induce more severe adverse effects than THC at relatively lower doses. In particular, acute administration of JWH-030 induced QT interval prolongation in the electrocardiogram. QT interval prolongation is a putative marker of arrhythmia. Therefore, these results suggest that SCRA-related sudden death may be related to QT prolongation and consequent arrhythmic events. Furthermore, SCRAs may cause cardiotoxicity through PAK1, which is associated with hypertrophy of the heart (Yun et al. 2016a; Yoon et al. 2019a, b;2020a, b). To the best of our knowledge, this is the first report on JWH-series cardiotoxicity. SCRAs also have adverse effects on immune function. JWH-21O reduced the cell receptor-CD3 complex and CD8 expression, which is related to T-cell development. These results suggest that SCRAs may induce dysfunction of normal immune responses against bacterial infections such as tetanus.

As reviewed in this article, SCRAs affect almost all the organs, as shown in Table 3, and they have a higher probability of causing lethal consequences than natural cannabinoids.

Conclusions

The abuse of NPS, such as SCRAs, has become one of the biggest concerns in modern society. The substances are considered distinct from most established illicit drugs because they were originally designed as legal alternatives for controlled substances (King and Kicman 2011). Although various legal actions to control NPS have been introduced and implemented, new substances continue to appear to avoid existing control measures. This further complicates the situation as the prediction of the changes in the NPS market will become more difficult as there are continuously new attempts to seek novel psychological experiences. Even though many SCRAs have been scheduled by analog scheduling measures in some countries, novel compounds are still

Table 3 Adverse effects of SCRAs on organs (18–1, 29, 50)

Organ	Adverse effects
Cardiovascular system	Tachycardia, hypertension, arrhythmia, myocardial infarction, cardiac arrest
Respiratory system	Acute respiratory depression
Urinary system	Acute tubular necrosis, interstitial nephritis, rhabdomyolysis
Gastrointestinal system	Nausea, vomiting, changes of gut microbiota
Immune system	Changes in the immune system development, alterations of the hypothalamus–pituitary–adrenal axis functions, T-helper subpopulation reduction
Central nervous system	Agitation, irritability, catatonia, seizures, sedation, memory loss, psychosis, anxiety, panic, suicidality, self-injury, psychological or physical dependence

SCRA synthetic cannabinoid receptor agonists

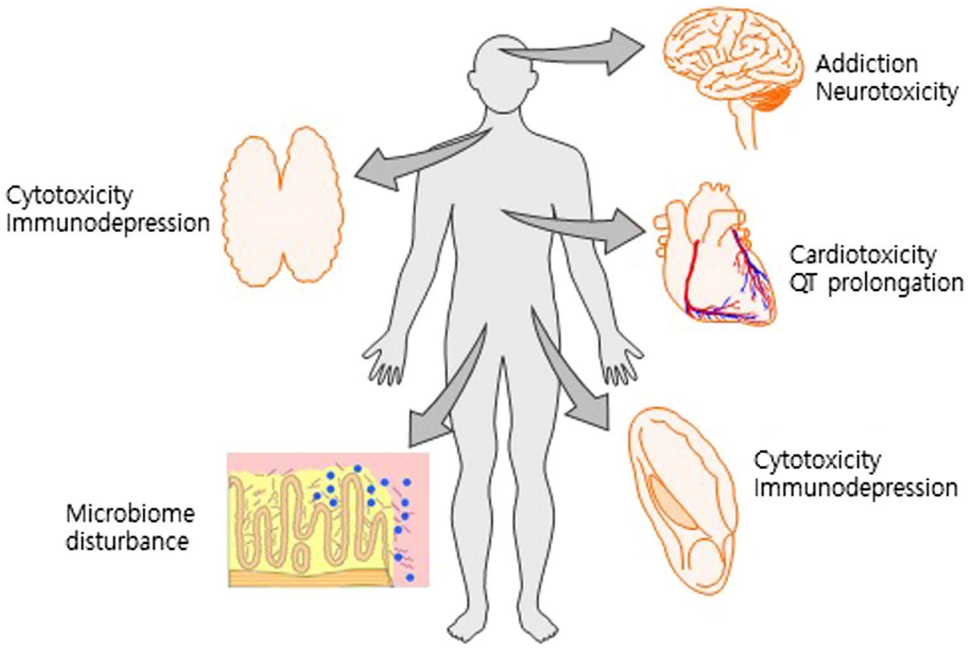

Fig. 5 Principal adverse effects on the human body by SCRAs

emerging and jeopardizing people's lives (Peacock et al. 2019a). In this review, the negative implications of SCRAs on the human body are summarized in Fig. 5.

Globalization and advancements in communication have accelerated the spread of NPS. However, these can also be useful to develop new legislative strategies and distribute educational or informative materials regarding the dangers of these compounds. To achieve these goals, it is important to accumulate scientific data continuously and provide exact information on the harmfulness of these substances. In line with sharing information, the development of new methodologies is also needed to evaluate the pharmacological and toxicological properties of NPS more effectively. When the pharmacological and toxicological characteristics of NPS are fully understood, effective strategies for control, prevention, and treatment could then be successfully implemented.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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