Predicting the Abuse Liability of Entactogen-Class, New and Emerging Psychoactive Substances via Preclinical Models of Drug Self-administration

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Abstract Animal models of drug self-administration are currently the gold standard for making predictions regarding the relative likelihood that a recreational drug substance will lead to continued use and addiction. Such models have been found to have high predictive accuracy and discriminative validity for a number of drug classes including ethanol, nicotine, opioids, and psychostimulants such as cocaine and methamphetamine. Members of the entactogen class of psychostimulants (drugs that produce an "open mind state" including feelings of interpersonal closeness, intimacy and empathy) have been less frequently studied in self-administration models. The prototypical entactogen 3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy") supports self-administration but not with the same consistency nor with the same efficacy as structurally related drugs amphetamine or methamphetamine. Consistent with these observations, MDMA use is more episodic in the majority of those who use it frequently. Nevertheless, substantial numbers of MDMA users will meet the criteria for substance dependence at some point in their use history. This review examines the currently available evidence from rodent self-administration studies of MDMA and two of the new and emerging psychoactive substances (NPS) that produce entactogen type neuropharmacological responses – mephedrone (4-methylmethcathinone; 4MMC; "meow meow") and methylone (3,4-methylenedioxymethcathinone). Overall, the current evidence predicts that these NPS entactogens have enhanced abuse liability compared with MDMA.

Keywords Addiction • Drug abuse • Empathogen • Entactogen • MDMA • Mephedrone • Methylone • Self-administration

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1 Current Epidemiology of Entactogen Use

The term "entactogen" is used to delineate recreational drugs that "produce experiences of emotional communion, oneness, relatedness, emotional openness – that is, empathy or sympathy" [1] or, as originally coined by Nichols, a drug that "powerfully enhances emotions and empathy" [2]. Although (±)3,4-methylenedioxyamphetamine (MDA) enjoyed some popularity through the mid-1980s, (±)3,4-methylenedioxymethamphetamine (MDMA) became the class-defining entactogen and has been the most common constituent of illicit "Ecstasy" [3] over recent decades. Epidemiological data from the Monitoring the Future (MtF) survey show that use of Ecstasy in high school students [4] has been stable in the past decade while annual prevalence rates for college students have gradually increased [5]. Annual prevalence of MDMA/Ecstasy in individuals in their 20s is equivalent to that for non-crack cocaine, slightly lower than for all amphetamines (including ADHD medications) and is at least threefold higher than prevalence of heroin, crack (smokable cocaine), ice (smokable methamphetamine), or phencyclidine. The MtF data also report that 17% of 29- to 30-year-olds and 10–14% of 21- to 28-year-olds have used MDMA at least once in their lifetime [5]. Thus, overall lifetime rates of recreational exposure to MDMA are substantial and will continue to be so for some time as these cohorts age. Further exposure may result from the initiation of multiple Phase I clinical trials to establish MDMA as an adjunctive treatment for psychotherapy nearly a decade ago [6–9], although results remain controversial [10–12]. Overall, the impact of MDMA on health continues to be a pressing issue for scientific investigation.

Greer, arguing for the use of MDMA (50–200 mg) in psychotherapy [13], claimed that MDMA has low abuse liability because its use is self-limiting (reduction in desirable effects and an increase in adverse effects with continued use) and some subsequent studies have indicated spontaneous disuse with time [14, 15], a transition that has been speculated to reflect lasting changes in brain serotonergic function. Nevertheless, significant proportions of heavy Ecstasy users meet criteria for dependence at some point in their use history [16–18] and there are case reports of Ecstasy use patterns that are daily or at least several times per week [19–21]. These latter examples are highly consistent with the repetitive use patterns

that are common to reference drugs of abuse such as methamphetamine (METH), cocaine, and heroin. Similarly, close examination of Ecstasy use statistics in human cognitive/toxicity investigations identifies occasional (rare) individuals who use Ecstasy at least several times per week [22–28], which stands in contrast to studies of METH-related cognitive impairment in which *most* individuals are using 3 times per week or more [29–31]. It is also clear that Ecstasy consumers abuse a very wide range of drugs with some frequency [32, 33], suggesting a level of generalized substance dependence that may be elevated in those that use MDMA [34]. The evidence for human Ecstasy dependence has grown to the point where efforts are underway to establish criteria for a new MDMA-specific DSM diagnostic category [35, 36].

Recreational use of *cathinone* derivative stimulant drugs ("bath salts") is new but has increased substantially since 2009 and continues to expand worldwide. Some of the earliest appearing and most popular entities such as 4-methylmethcathinone (4MMC; *mephedrone*) and 3,4-methylenedioxymethcathinone (*methylone*; beta-keto-MDMA) were explicitly marketed as MDMA substitutes and are reported to have MDMA-like, entactogen-characteristic subjective effects [37, 38]. Use of mephedrone expanded rapidly in the UK from 2009 to 2010 [38, 39] during a reported European shortage of MDMA [40, 41]. Mephedrone and methylone appear to have sustained popularity despite legal controls [42] and have joined drugs such as MDMA or cocaine, rather than replacing them, in user populations [43]. Just as up to 40% of Ecstasy users may meet criteria for dependence [44], there is initial evidence of dependence on mephedrone [45, 46]. The 2013 and 2014 midyear reports of the US National Forensic Laboratory Information System [47, 48] show that methylone is now more common than MDMA in this database and case reports of fatalities involving mephedrone or methylone are highly reminiscent of similar deaths attributed to MDMA [49–53]. The emergence of these new, MDMA-like recreational drugs has prompted controlled, laboratory studies to determine the potential similarities and differences among these entactogens, including studies of relative abuse liability.

2 Entactogen Pharmacology and Predicted Addiction Liability

It is perhaps obvious that a recreational drug such as MDMA that exhibits distinct subjective properties compared with the structurally related prototypical psychostimulant METH would have different pharmacological and neurochemical properties. For example, in vitro investigations by several groups [54–58] show that methylone and mephedrone are monoamine transporter substrates, which act to enhance transporter-mediated release of monoamines as do both MDMA and METH, in vivo. However, mephedrone [54, 59, 60] and methylone [54, 61] each produce neuropharmacological profiles of enhanced release of serotonin (5-HT)

compared to dopamine (DA) in the nucleus accumbens, similar to MDMA but dissimilar to METH. Thus, the key distinction in overall subjective effects between METH and the entactogens appears to be the relative effects on 5-HT transporters (SERT) versus DA transporters (DAT), and ensuing monoaminergic signaling.

The in vitro pharmacological data likewise show that the entactogens are dissimilar to a typical stimulant such as METH. Simmler and colleagues report a DAT/SERT ratio on transporter inhibition of 0.08 for MDMA, 1.4 for mephedrone, and 3.3 for methylone versus >10 for METH, using human transporters expressed in cells. DAT inhibition potency (IC_{50}) was 17 μM for MDMA, 4.82 μM for methylone, and 3.31 μM for mephedrone, compared with 1.05 μM for METH. Finally, an assay of monoamine release mediated by the DAT illustrates an effective concentration (EC_{50}) of 3.75 μM for mephedrone, 22 μM for MDMA, >100 μM for methylone, and 1.56 μM for METH. MDMA and mephedrone were about equipotent at inhibiting 5-HT release mediated by the SERT (5.63 μM and 5.98 μM, respectively); however, the EC_{50} for methylone was >10 μM compared to >33 μM for METH. An analysis of transporter-mediated monoamine release using rat brain synaptosomes [54] reported that the DAT/SERT ratios of the entactogens (mephedrone 2.41; methylone 1.82; MDMA 0.97) were much lower than that of METH (152.0). In summary, the in vitro pharmacological data and the in vivo neuropharmacological data predict that the entactogens would exhibit similar abuse liability, but these drugs would exhibit *less* propensity for repetitive use compared with a traditional stimulant drug like METH.

When it comes to controlled laboratory models of abuse liability such as the intravenous self-administration (IVSA) procedure, the relative DA/5-HT effects have been thought most critical. In short, relatively enhanced 5-HT effects tend to reduce the degree to which rats or monkeys will self-administer a given drug [62–64]. These findings are reinforced by demonstrations that drugs which function as 5-HT indirect agonists suppress the rate of cocaine or amphetamine self-administration in monkeys [62, 65, 66] and that exposure to a 5-HT depleting regimen of MDMA in rats enhances acquisition of the self-administration of cocaine [67] and enhances reinstatement of D-amphetamine seeking primed by either D-amphetamine or MDMA [68]. The correlation of DA/5-HT potency ratios with reinforcer efficacy agrees with a finding that prior treatment of rats with the serotonergic neurotoxin 5,7-dihydroxy-tryptamine [69] or genetic deletion of the SERT [70] enhances the acquisition of MDMA IVSA. Nevertheless, the idea of relative DAT/SERT selectivity as a major determinant of abuse liability is a dogma that was established before the emergence of the cathinones, with MDMA as the lone example of an entactogen that was popular with human users. The emergence of the two cathinone-class entactogen drugs mephedrone and methylone has provided a key opportunity to further determine abuse liability of designer stimulant drugs.

3 Self-administration of Entactogens

3.1 Overview of Methods

Drug self-administration is a powerful preclinical/non-clinical method for predicting the abuse liability of that drug [71]. Various self-administration procedures provide methods to quantify the rewarding capacity of different recreational drugs. If delivery of a drug can increase the frequency or probability of a behavioral response (such as a lever press) from a laboratory animal, it is considered to act as a reinforcer of that behavior; this capacity features prominently in the processes theorized to lead to addiction [72]. In general, the greater the efficacy of a drug as a reinforcer in laboratory animal self-administration procedures, the higher its potential abuse liability is predicted to be for humans.

Self-administration can therefore be used to evaluate the reinforcer efficacy and potency of new and emerging psychoactive substances (NPS) for which little, if any, human epidemiological data are available. Moreover, once a drug has been shown to be efficacious as a reinforcer, self-administration procedures can be used to determine the neurobiological, behavioral, or environmental determinants of drug taking behavior. For drugs that have highly variable use patterns and/or inconsistent/conflicting reports of abuse, the self-administration paradigm can be used to determine the conditions that increase reinforcer potency and efficacy.

Importantly, the most basic rodent self-administration procedure (i.e., lever pressing under a fixed-ratio schedule for the intravenous delivery of drug over a short 1–2 h access interval) is not a model of drug abuse or addiction – rather, it models drug reward and reinforcement [73]. It is clear, however, that reward or reinforcement processes contribute to, or are a component of, the phenomena outlined as being diagnostic of drug abuse/addiction [i.e., as defined by either the DSM5 (USA) or ICD10 (Europe)]. Under certain conditions, self-administration in an animal model may result in behavior that would meet the human diagnostic criteria (see below). Even if an animal's self-administration of a drug under the typically short periods of drug access does not constitute the expression of disordered use or addiction per se, the capacity of drugs to support self-administration has valuable and well-validated predictive utility [71, 74, 75].

There are two primary methods to determine the potential of a given drug to reinforce self-administration behavior. First and most simply, assessment of the initial acquisition of drug taking behavior can be used to quantify how rapidly and readily drug availability comes to support behavioral responding. This can be used to determine the threshold dose that is necessary to produce a behaviorally reinforcing effect, providing an estimate of drug potency. Comparison of different patterns of responding across drugs can provide additional insight; for example, the inter-session and intra-session variability in MDMA intake is relatively high [76] compared with METH. Similarly, comparison of the initial acquisition of responding for drug infusions can illustrate inter-individual variation in reinforcing value; for example, only about half of subjects meet criteria for MDMA self-

administration, whereas virtually all acquire cocaine self-administration [77]. Drug acquisition can also vary across environmental and other contexts; for example, when alternative reinforcers are available (e.g., palatable food, wheel access), this may differentially alter responding for intravenous drug infusions [78].

A second way to assess the reinforcing capability of different drugs is by comparing dose–response curves under varied schedules of reinforcement, following initial acquisition. This involves varying the available per-infusion dose of the drug from session to session to determine how the animal alters its response pattern. In the simplest version, a fixed ratio (FR; each successive infusion within a session requires a fixed number of responses) schedule of reinforcement is typically used to determine potency (i.e., minimum amount of drug required to maintain responding). A more complex approach is the use of a *progressive* ratio (PR) schedule of reinforcement in which the number of responses required to obtain each successive infusion increases within the session. The PR procedure is typically used to determine efficacy (i.e., the maximum amount of responding the drug can support at a given dose) [79–81]. Alternatively, systematic within-session reductions in the available per-infusion dose to zero while under a fixed-ratio schedule can also permit calculation of the maximum amount of responding that the drug will support [82]. Both this within-session thresholding procedure and the PR approach are in essence a protracted transition to an extinction condition and as such it should be the case that the response rate drops to zero as either the response number becomes too high (PR) or the dose drops too low (within-session thresholding) [83, 84].

Additional modifications of the basic self-administration procedure that extend the model to address various DSM5/ICD-10 diagnostic criteria for substance abuse and/or addiction include:

1. The extended access model which usually compares self-administration sessions that are relatively short to ones that are long (e.g., 1–2 h vs. 6 h – typical for cocaine or methamphetamine) to study the phenomena of intake escalation [85–87].
2. The inclusion of adverse consequences or punishments – for example, foot shock [88–90] or histamine administration [91–93] – to study the phenomena of drug taking despite incurring negative outcomes.
3. Reinstatement of responding following its extinction by re-exposure to the drug, presentation of drug-paired cues, or exposure to a stressor to study the phenomena of relapse [94–97].
4. Making alternative "natural" reinforcers available to study the phenomena of devaluation of non-drug rewards and preoccupation with drug seeking [98–100].

3.2 MDMA

It has been repeatedly demonstrated that METH or amphetamine will readily support intravenous self-administration (IVSA) in rats [101–105], nonhuman

primates (NHPs) [106–110], and cats [111]. Laboratory studies of the abuse liability of MDA or MDMA have been curiously sporadic in comparison with the typical amphetamines, perhaps because the "average" non-compulsive human use pattern does not appear to fit well with the usual animal models. While it is clear that MDA [112] or MDMA [107, 113–116] will substitute for cocaine in baboons and rhesus monkeys trained for intravenous self-administration, it has yet to be established that drug-naïve nonhuman primates will acquire MDA or MDMA self-administration by any route of administration, or that oral administration of either drug will function as a reinforce, even in drug-experienced NHPs.

Interpretation of entactogen IVSA in rats is complicated by a broad range of individual differences in drug preference compared with the IVSA of other stimulants, a relative dearth of studies and the methodological and analytical choices of authors in conducting their studies. One available study showed that rats will self-administer MDA (~0.3 mg/kg/inf) under fixed-ratio 1 (FR1) training conditions, but behavior was extinguished under progressive-ratio (PR) conditions [117]. Additional studies show that MDMA generates consistent levels (2–5 mg/kg/session) of self-administration in rats [118–123], although one laboratory report intakes several fold higher [76, 124, 125]. It is clear from the available evidence that rat IVSA of MDMA differs from the IVSA of typical psychostimulants such as cocaine, amphetamine, or METH. Dalley and colleagues [102] reported highly variable MDMA (50 μg freebase per infusion; ~0.15 mg MDMA HCl/kg/inf; 32–50 infusions over session) IVSA compared with either amphetamine or METH (same dose, 60–75 infusions with greater day to day stability) in rats that were food restricted. Schenk and colleagues have shown that only about 55–60% of individuals will reach acquisition criteria for MDMA IVSA within about 10–14 training sessions using a protocol which starts at 1 mg/kg/inf and then is reduced to 0.5 mg/kg/inf [70, 77], suggesting that subject inclusion criteria may partially contribute to differential results between laboratories. The critical effect of subject inclusion criteria was highlighted by work in which a median-split was presented for acquisition data instead of excluding subjects on arbitrary acquisition criteria [120, 123]. In particular, when rats were subjected to dose-substitution studies under an FR-1 response contingency, the less-preferring half of the distributions of male and female rats were probably not self-administering MDMA since they were insensitive to changes in the available dose.

Serotonergic dysfunction produced by either SERT deletion or a 5-HT selective neurotoxin [69, 70] dramatically increases the percent of animals reaching acquisition criteria for MDMA self-administration. In essence, these manipulations make the neuropharmacological response to MDMA more similar to that of METH which would provide one possible mechanistic explanation for the enhanced reinforcer efficacy of MDMA in such studies. In a similar vein, the ~50% of animals that met acquisition criteria for IVSA of MDMA are insensitive to antagonists of the 5-HT 1A, 1B or 2A receptor subtypes [126], possibly indicating that the half of the distribution of rats that acquire MDMA IVSA are constitutively less sensitive to the serotonergic effects of MDMA.

Lack of a systematic approach to methodological variables in reports published so far has further complicated the comparison of MDMA IVSA data with data from the broader number of studies involving METH or cocaine self-administration. For example, while studies hint that increases in MDMA intake, and the number of subjects who meet acquisition criteria, may be achieved through exposure to many sessions of access [102, 121, 127, 128], this issue has not been comprehensively explored. Other methodological variables also may be critical. For example, one report [129] demonstrates that acute increases in ambient temperature (30°C) significantly enhance self-administration of MDMA, though consistent training under elevated temperature conditions may not have any effect [130]. Additional variables which can affect self-administration include: rat strain, time of day in which sessions are conducted [131], the speed of the intravenous infusion [121], housing enrichment [132], and food restriction [102].

Relatively few studies have specifically examined MDMA IVSA under short vs long daily access conditions. This latter approach has been proposed to better reflect the transition to dependence [85, 86]. Vandewater and colleagues found that 6 h MDMA (0.5 mg/kg/inf) IVSA led to increased intake compared with 2 h sessions in male rats [123] which is consistent with the "escalated" intake reported for cocaine or METH. This finding was inconsistent with a prior report that 6 h access led to no difference in *total session MDMA intake* relative to rats trained in 2 h sessions [76], but that outcome may have depended on a relatively high per-infusion dose (1.0 mg/kg/inf) and/or training animals in the inactive (light) cycle. Additional targeted study would be required to resolve conditions under which MDMA self-administration does, or does not, escalate with longer daily access.

It has long been established that significant sex-differences exist in rat models of stimulant drug abuse. For example, female rats will self-administer more cocaine [133, 134] and more METH [135, 136] than males, and these sex differences can be more pronounced under long-access escalation and/or progressive ratio procedures. In the single study of MDMA IVSA in *female* rats that is currently available [120], the authors found that female rats showed only a slightly more consistent MDMA intake when directly compared with male rats under 2 h daily access conditions (see the Supplemental Materials of [123]). Escalation of self-administration of MDMA in females under longer access conditions has not yet been examined.

3.3 Mephedrone and Methylone

The original report of mephedrone IVSA in rats indicated that it can readily support IVSA [137]; however, the study was limited to a single per-infusion dose and access conditions that likely increased drug intake. Specifically, access to drug was relatively long (4 h) and under high (29°C) ambient temperature (T_A). As noted above, escalation of METH intake occurs when daily drug access is 6 h vs 2 h [138] and intake of cocaine, METH, and MDMA increase under relatively high (30°C vs. ~22°C) T_A conditions [129, 139]. Hadlock and colleagues also compared the

IVSA of mephedrone with IVSA of a similar per-infusion dose of METH and found greater intake of mephedrone. However, equipotent per-infusion doses are essential for comparison of numbers of infusions, since higher doses generate fewer infusions [138]. Subsequent work showed mephedrone to be less potent than METH in other assays [54, 60, 140]; thus, the initial report may have overestimated mephedrone IVSA relative to METH IVSA. Aarde and colleagues [101] showed that mephedrone supports IVSA similarly in both Wistar and Sprague–Dawley rats and that a training dose of 0.5 mg/kg per infusion supported approximately as many reinforcer deliveries as METH at a dose of 0.05 mg/kg per infusion. Motbey and colleagues [141] found that adolescent male Sprague–Dawley rats obtained a mean of about 60 infusions of mephedrone (0.3 mg/kg/inf) after 10 sessions, also suggesting it is a highly efficacious reinforcer in IVSA. Unfortunately, there are no other entactogen IVSA data in adolescent animals to place these data in context. Two additional studies directly compared the IVSA of mephedrone and MDMA and found that the mephedrone was a more efficacious reinforcer than MDMA, resulting in higher daily intakes of drug [120, 123].

The first examination of methylone IVSA showed robust acquisition of self-administration, with all rats reaching criteria at the 0.5 mg/kg/infusion training dose and breakpoints under a PR procedure similar to those reached by METH trained rats in 2-h access sessions [142]. Subsequent studies indicated a less-efficacious profile for methylone. Direct comparisons of methylone-trained male or female rats with those trained on MDMA or mephedrone showed the greatest intakes for mephedrone, the lowest for MDMA, and an intermediate profile for methylone [120, 123, 143]. Schindler and colleagues [61] found that male Sprague–Dawley rats showed methylone IVSA to about the same extent as Vandewater et al. [123], again in 2-h access sessions. A potential bridge across these studies was provided by an indication that training male rats in 6 h daily access sessions resulted in greater escalation of drug intake for methylone than for MDMA [123, 143]. These results suggest that as yet undetermined methodological differences may explain the differences in outcome between the study of 2 h access IVSA [61, 123, 142]. Nevertheless, the evidence at present suggests that methylone is most likely a more efficacious reinforcer than MDMA.

With respect to sex-differences, Creehan et al. [120] showed that female rats readily acquired IVSA of methylone; however, a follow-up study from the same group [123] demonstrated a similar relative abuse liability in male rats. Rats of both sexes reached a mean of about 12–15 infusions of methylone after 10 sessions of acquisition training, as compared to about 7–10 infusions of MDMA (0.5 mg/kg/inf) and 20–25 infusions of mephedrone (0.5 mg/kg/inf) in separate groups of male and female rats.

In summary, initial reports from rat IVSA studies indicate mephedrone and methylone exhibit readily established and relatively *consistent* self-administration profiles [137, 141, 142] that appear to contrast with the less reliable profile that has been established for MDMA. This conclusion was underlined most directly in studies that compared the three entactogens within a single model [120, 123, 143].

3.3.1 Future Directions

As this review has shown, there are relatively few investigations of the abuse liability of entactogen psychostimulants. Much is still to be identified about their properties, but there are nevertheless a few key issues which are of the most pressing importance for the field. The first three are relatively general: (1) study of sex-differences, (2) ability to rapidly screen novel cathinone derivatives, and (3) non-rat models of abuse liability. The remaining issues are specific to understanding why the entactogen cathinones appear to have enhanced abuse liability relative to MDMA (pharmacokinetics, speed of monoamine responses and non-monoamine pharmacological properties). These issues are discussed in further detail below.

3.3.2 Sex-Differences

The US National Institutes of Health (NIH) has recently issued a policy position which reinforces the critical importance of conducting sex-difference comparisons across biomedical domains [144]. The importance of this new initiative is certainly apparent for substance abuse research since substance use increases more quickly in women and treatment outcomes are poorer compared with men [145, 146]. METH dependence starts earlier in women [147, 148], cocaine treatment outcomes are less successful [145], and MDMA dependence occurs more frequently in women [46, 149]. It has been shown that female rats will self-administer more cocaine [133, 150] and more METH [135, 136] than male rats but, as mentioned briefly above, there is only one study of the self-administration of any entactogen in female rats that has been reported to date [120]. While that study found minimal sex-differences, it must be emphasized that this single study only begins to address the scope of work necessary for firm conclusions about potential sex-based differences.

3.3.3 Generalization or Rapid Screening

One of the clearest challenges with the cathinone derivative drugs is the diversity of the molecules which have entered recreational use markets. Driven by efforts to stay one step ahead of legal controls, the suppliers for recreational users have proven agile in providing a number of different compounds across place and time. This diversity poses a significant challenge for the research efforts to determine relative risks, and this concern is particularly acute for the relatively labor-intensive IVSA procedure. Dose-substitution tests of multiple drugs in a single group of rats is possible [120, 123], albeit this can be limited due to concerns over sequence effects and useful catheter life. Such attempts are very rare in rats for any drug class, but are much more common in nonhuman primate models, as reviewed

[151]. Additional participation in evaluating novel and emerging psychoactive substances from the many laboratories which use IVSA models to study the reinforcing properties of psychostimulants would be helpful in this regard.

3.3.4 Self-administration in Nonhuman Primates and Mice

No data are available on the self-administration of the entactogen cathinones in nonhuman primate or mouse models at present. Extension of research on the cathinones to these other relatively common self-administration models would facilitate deployment of the powerful genetic tools available with mouse models and would allow identification of any order differences in NHP models which might complicate translation to the human condition.

3.3.5 Pharmacokinetics

One key drug property which may differentiate mephedrone, methylone, and MDMA is the relative speed of brain entry, metabolism, and elimination. Rapid onset and offset of drugs is associated with more frequent re-dosing and transitions to habitual behavior. One study suggested that mephedrone may cross the blood–brain barrier more quickly than does MDMA [57], which may partially explain its enhanced efficacy as a reinforcer. A study conducted in humans found a 3.6-fold slower elimination half-life for MDMA compared with mephedrone after oral dosing [152] and methylone exhibits a 2.5-fold slower half-life compared with mephedrone after i.v. administration in rats [153, 154]. Humans variously self-administer entactogens orally, by insufflation, by intravenous injection, with e-cigarette "vape" inhalation and occasionally via rectal or vaginal routes so further understanding of how route of administration may affect pharmacokinetic profiles may be important.

3.3.6 Neuropharmacological Differences

Differences in the rapidity of the accumulation of extracellular DA versus 5-HT following injection of mephedrone and MDMA have been identified using intracerebral microdialysis techniques [59] although the 20 min sampling of that study gives poor temporal resolution. The reason for this difference is unknown at present and further investigation could help to clarify the predictive value of the relative temporal character of DA versus 5-HT responses. Since humans variously use entactogens by intravenous injection, insufflation, the oral route, and other methods, additional questions arise about the relative DA/5-HT responses in the context of different routes of administration.

3.3.7 Non-monoamine Targets

Although clearly the DA and 5-HT responses to the entactogens confer the majority of the signal when it comes to reinforcing and rewarding properties, it is always possible that subtle non-monoamine properties may differentiate these compounds. For example, a sigma1 affinity of mephedrone has been reported [155] and an agonist at this site would be predicted to enhance self-administration [156]. Additional study of the potential modulatory effects of non-monoamine neuropharmacological responses to various cathinone-derivative NPS would significantly advance understanding.

4 Discussion

It is clear that the relative neuropharmacological responses of DA and 5-HT in the nucleus accumbens of the rat are insufficient to completely predict the abuse liability of entactogen-class psychostimulants. Similarly, other preclinical models of abuse liability may not generate the best predictions. For example, Bonano and colleagues concluded that the lower potency of mephedrone to decrease intracranial self-stimulation reward (ICSS) thresholds [157] compared with methylone suggested that it would have lower abuse liability. Relatedly, mephedrone and methylone produce similar dose–response functions for locomotor stimulation in mice and identical potencies in a drug-discrimination assay when rats are trained on cocaine; however, methylone was less potent in METH-trained rats [158]. Thus, the most precise preclinical predictor of relative abuse liability for the entactogens will continue to be the self-administration procedure.

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