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# MEPHEDRONE ("BATH SALT") PHARMACOLOGY: INSIGHTS FROM INVERTEBRATES

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**Abstract—Psychoactive bath salts (also called meph, drone, meow meow, m-CAT, bounce, bubbles, mad cow, etc.) contain a substance called mephedrone (4-methylcathinone) that may share psychostimulant properties with amphetamine and cocaine. However, there are only limited studies of the neuropharmacological profile of mephedrone. The present study used an established invertebrate (planarian) assay to test the hypothesis that acute and repeated mephedrone exposure produces psychostimulant-like behavioral effects. Acute mephedrone administration (50–1000 μM) produced stereotyped movements that were attenuated by a dopamine receptor antagonist (SCH 23390) (0.3 μM). Spontaneous discontinuation of mephedrone exposure (1, 10 μM) (60 min) resulted in an abstinence-induced withdrawal response (i.e. reduced motility). In place conditioning experiments, planarians in which mephedrone (100, 500 μM) was paired with the non-preferred environment during conditioning displayed a shift in preference upon subsequent testing. These results suggest that mephedrone produces three behavioral effects associated with psychostimulant drugs, namely dopamine-sensitive stereotyped movements, abstinence-induced withdrawal, and environmental place conditioning.** 

**Key words: mephedrone, withdrawal, dopamine, motility, place preference, planarians.**

Mephedrone [4-methylmethcathinone] is a synthetic compound of the amphetamine and cathinone classes that has emerged as a popular street drug in Europe and the USA (Winstock et al., 2010). Although the legal status of mephedrone varies between governed entities, it is available for purchase over the Internet and is often marketed as "plant feeder," "bath salts," "research chemicals," and "not for human consumption." Factors contributing to its popularity are ease of online accessibility, extensive web-based marketing, versatile administration route (intranasal, oral), high degree of purity, and high yields from simple manufacturing processes that utilize inexpensive precursors (Schifano and Corkery, 2008). Initial evidence of human mephedrone use appeared online in 2007 (Psychonaut Web Mapping Research Group, 2009). Most of what is currently known about mephedrone has been obtained from analyses of online discussions, single case reports, and small-scale focus groups (Meyer et al., 2010; Wood et al., 2010). The broadest human study to date focused on experienced drug users in the United Kingdom (Winstock et al., 2010, 2011). In that study, mephedrone was the sixth most frequently used drug (41.3% of 2295 participants) after nicotine, alcohol, cannabis, cocaine, and 3,4-methylenedioxymethamphetamine (MDMA). Evidence from human users suggests that mephedrone elicits a longer-lasting and better high than cocaine (Winstock et al., 2010). Further evidence suggests that mephedrone elicits euphoria and sociability without causing a hangover and produces a smoother high than MDMA (Newcombe, 2009). Risks of mephedrone use include toxicity (cardiac events, manganese toxicity, parkinsonian syndrome, etc.), lethality, and polydrug abuse (Al-Motarreb et al., 2010; Stepens et al., 2008).

Studies examining the pharmacological profile of mephedrone have begun to emerge. Mephedrone increases extracellular dopamine and serotonin in the mesolimbic system of rats through inhibition of dopamine and serotonin reuptake, and it is self-administered by rats (Kehr et al., 2011; Hadlock et al., 2011; Martínez-Clemente et al., 2012). In the present study, we characterized the *in vivo* behavioral effects of mephedrone in planarians, a type of aquatic flatworm that has a centralized nervous system, which some consider the simplest "brain" (Raffa and Rawls, 2008; Rawls et al., 2011). Planarians contain neurotransmitter systems, including glutamate, dopamine, serotonin, acetylcholine, and gamma-aminobutyric acid (Eriksson and Panula, 1994; Vyas et al., 2010; Nishimura et al., 2010), and to a limited extent display mammalian-equivalent behavioral responses (enhanced stereotypical activity, abstinence-related withdrawal, behavioral sensitization, cross sensitization, and conditioned place preference) following exposure to addictive substances from different drug classes (Palladini et al., 1996; Pagán et al., 2008, 2009; Rowlands and Pagán, 2008; Raffa and Rawls, 2008; Rawls et al., 2010a,b, 2011). The current experiments characterized mephedrone using three behavioral endpoints: acute stereotypical activity and its sensitivity to dopamine receptor antagonism; abstinence-induced with-

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*Abbreviations:* MDMA, 3,4-methylenedioxymethamphetamine; MEPH, mephedrone; VEH, vehicle.

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drawal following discontinuation of mephedrone exposure; and environmental place conditioning.

## EXPERIMENTAL PROCEDURES

### Subjects and Drugs

Planarians (*Dugesia dorotocephala*) were purchased from Carolina Biological Supply (Burlington, NC, USA). Upon arrival in the laboratory, planarians were maintained in the aqueous solution provided by Carolina Biological Supply, acclimated to room temperature (21 °C), and tested within 3 days of receipt. (R,S)-mephedrone was obtained from the Fox Chase Chemical Diversity Center (Doylestown, PA, USA). SCH 23390 ((R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride) was obtained from Tocris Bioscience (St. Louis, MO, USA). Stock solutions of each drug were prepared daily in a vehicle of tap water containing AmQuel® water conditioner. Treatment solutions were diluted with tap water containing AmQuel® water conditioner (1 ml Amquel per 1 gal of water).

### Behavioral studies

*Experiment 1: Does acute mephedrone exposure produce dopamine-sensitive stereotyped movements?* Individual planarians were placed randomly into a transparent petri dish (5.5 cm diameter) containing a solution of mephedrone (0, 10, 50, 250, 100, 500, 1000 $\mu$M) for 10 min. Stereotyped movements were quantified as the number of C-like hyperkinesias during the 10-min exposure (Rawls et al., 2011; Raffa et al., 2010). Motility counts during the 10-min exposure interval were also quantified as the number of gridlines crossed, or re-crossed, by placing the petri dish over graphing paper with gridlines spaced 0.5 cm apart (Sacavage et al., 2008; Raffa and Valdez, 2001). For combined administration, stereotyped movements were quantified during a 10-min exposure to vehicle, SCH 23390 (0.3 $\mu$M), mephedrone (500 $\mu$M), or a combination of SCH 23390 (0.3 $\mu$M) (10-min pretreatment) and mephedrone (500 $\mu$M). The concentration of SCH 23390 was selected on the basis of its reported Ki values, which are 0.2 nM and 0.3 nM at $D_1$ and $D_5$ receptor subtypes, respectively (Bourne, 2001).

*Experiment 2: Does the condition of mephedrone abstinence elicit a withdrawal response?* A characteristic withdrawal response displayed by planarians following discontinuation of exposure to an addictive substance is reduced motility (Raffa and Valdez, 2001). Individual planarians pretreated for 60 min with mephedrone (1 $\mu$M) or vehicle were placed for 5 min into a petri dish (5.5 cm diameter) containing mephedrone (1 $\mu$M) or vehicle and motility experiments were conducted as described earlier in the text. The experiment was repeated with 10 $\mu$M mephedrone.

*Experiment 3: Does mephedrone conditioning shift planarian environmental preference?* Dark and "ambient" light environments were created by covering half (top and bottom) of a petri dish with black paper, and individual planarians were placed at the midline of the dish. The time spent in the non-preferred environment (light) over a 5-min interval was determined (pre-pairing response). Planarians were then conditioned with mephedrone (0, 10, 100, 500 $\mu$M) for 30 min in the non-preferred environment. Immediately following conditioning, planarians were placed back at the midline of a petri dish (half light and half dark) containing vehicle, and the time spent in the original non-preferred environment over a 5-min interval was determined (post-pairing response).

### Data analysis

Comparisons of group means (±SEM) were evaluated by one-way ANOVA followed by Tukey's post hoc analysis or, for the environmental preference experiment, a two-way ANOVA (treatment, conditioning) followed by a Bonferroni test for multiple comparisons. Values of $P<0.05$ were considered statistically significant.

## RESULTS

### Acute mephedrone exposure elicits stereotyped movements that are attenuated by a dopamine receptor antagonist

Effects of different concentrations (0, 10, 50, 100, 250, 500, 1000 $\mu$M) of mephedrone on stereotyped movements are expressed in Fig. 1A. Planarians exposed to vehicle did not display stereotyped behaviors. Acute mephedrone exposure produced stereotyped movements that resulted in an $E_{max.}$ of 62.0±5.3 and $EC_{50}$ of 251.1±36 (Fig. 1A). Planarian motility was significantly affected only by the two highest concentrations of mephedrone, 500 and 1000 $\mu$M, which attenuated motility by approximately 75% and 65%, respectively, relative to vehicle controls (106.1±13.6 motility counts/10 min) ($P<0.001$) (not shown).

For combination experiments with SCH 23390 (0.3 $\mu$M), a concentration of 500 $\mu$M mephedrone that produced a consistent, robust enhancement of stereotyped movements was selected (Fig. 1B). A significant main effect [$F(4,45)=21.3$, $P<0.0001$] was observed. SCH 233390 (0.3 $\mu$M) by itself did not produce stereotyped movements. Planarians exposed to mephedrone (500 $\mu$M) displayed a significant number of stereotyped movements compared with vehicle-treated planarians ($P<0.001$). Planarians pretreated for 10 min with SCH 23390 (0.3 $\mu$M) before co-exposure to a combination of SCH 23390 (0.3 $\mu$M) and mephedrone (500 $\mu$M) displayed 67% fewer stereotyped movements than planarians exposed only to mephedrone (500 $\mu$M) ($P<0.01$). The effect of SCH (0.3 $\mu$M) against a higher concentration (1000 $\mu$M) of mephedrone was less effective, with 37% fewer stereotyped movements observed in planarians treated with the drug combination ($P<0.05$, not shown). Simple co-exposure (without the pretreatment phase) of planarians to a combination of SCH 23390 (0.3 $\mu$M) and mephedrone (500 $\mu$M) resulted in 33% fewer stereotyped movements compared with mephedrone (500 $\mu$M) by itself ($P<0.05$, not shown). Mephedrone concentrations tested here did not cause lethality.

### Discontinuation of mephedrone exposure elicits a withdrawal response

A significant main effect was identified for the 1 $\mu$M mephedrone data set [$F(3,36)=25.0$, $P<0.0001$]. Planarians pretreated with mephedrone (1 $\mu$M) for 60 min and then tested in vehicle (MEPH/VEH) displayed lower motility counts compared with planarians subjected to three other experimental conditions (Fig. 2): (1) mephedrone-naive planarians tested in vehicle (VEH/VEH) ($P<0.001$); (2) mephedrone-pretreated planarians tested in mephedrone (MEPH/MEPH) ($P<0.001$); and (3) vehicle-pretreated planarians tested in mephedrone (VEH/MEPH) ($P<0.001$). Mephedrone-naive planarians (VEH/VEH) displayed motility

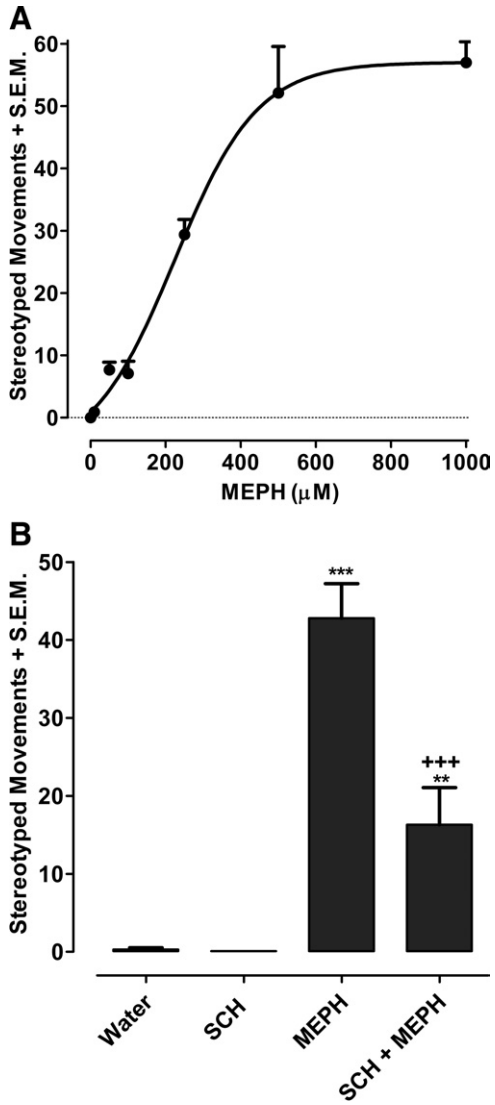


**Fig. 1.** Acute mephedrone (MEPH) exposure elicits dopamine-sensitive stereotyped movements. (A) Data are presented as the mean number of stereotyped movements+SEM quantified during a 10-min exposure to MEPH (0, 10, 50, 100, 250, 500, 1000 $\mu$M). $n$=8–10 planarians/group. (B) Data are presented as the mean number of stereotyped movements+SEM quantified during a 10-min exposure to vehicle (VEH), 0.3 $\mu$M SCH 23390 (SCH), 500 $\mu$M MEPH (MEPH), or 0.3 $\mu$M SCH+500 $\mu$M MEPH (SCH+MEPH). $n$=10 planarians/group. *** $P<0.001$, ** $P<0.01$ compared to VEH; $^{+++}P<0.01$ compared to MEPH.

counts that were not significantly different from mephedrone-pretreated planarians tested in mephedrone (MEPH/MEPH) (continuous exposure) or vehicle-pretreated planarians tested in mephedrone (VEH/MEPH) (acute exposure) ($P>0.05$). Similar results were obtained with a 10-fold higher mephedrone concentration (10 $\mu$M).

### Mephedrone conditioning causes a shift in environmental preference

A significant pairing effect was indicated by two-way ANOVA [$F(3,76)=4.644$, $P=0.0049$]. Planarians in which 100 $\mu$M mephedrone was paired with the non-preferred environment during conditioning displayed a 2.2-fold shift in preference ($P<0.05$). A higher concentration of mephedrone (500 $\mu$M) elicited a similar shift in preference ($P<0.01$). The percentage of planarians displaying a specific preference shift (10, 30, 60, and 120 s) as a function of mephedrone concentration is presented in Fig. 3B. Before mephedrone conditioning, 93% of planarians preferred the dark (Raffa et al., 2003).

## DISCUSSION

Mephedrone elicited a triad of behavioral effects in planarians that are characteristic of psychostimulant drugs. Those effects were dopamine-sensitive stereotyped movements following acute mephedrone exposure, a withdrawal response following discontinuation of mephedrone exposure, and a shift in environmental preference following mephedrone conditioning. The mephedrone effects were consistent with previously demonstrated effects of nicotine, cocaine, and amphetamine in planarians (Raffa and Rawls, 2008; Kusayama and Watanabe, 2000; Pagán et al., 2008, 2009).

Laboratory animals exposed to psychostimulant drugs often display stereotyped movements (Koob, 1992; Palladini et al., 1996; Buttarelli et al., 2000). In the current experiments, planarians displayed stereotyped movements following acute exposure to mephedrone. Mephedrone displayed similar efficacy, but greater potency, than nicotine (Rawls et al., 2011) and both greater efficacy and potency than cocaine (Rawls et al., 2010b). The nature of stereotyped movements in planarians, as well as their relation to stereotypical activity in rodents, is unclear despite evidence that both phenomena manifest during exposure to a common stimulus (acute stimulant exposure). Stereotyped movements in planarians

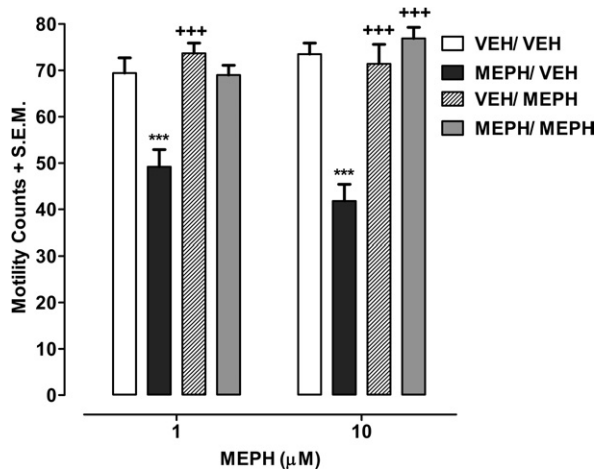


**Fig. 2.** The condition of mephedrone (MEPH) abstinence results in a withdrawal response. Planarians were subjected to the following paradigm (60 min pretreatment/5 min test): (VEH/VEH); (MEPH/VEH); (VEH/MEPH); and (MEPH/MEPH). Data are presented as the mean number of motility counts+SEM during the 5-min test period. $n$=10 planarians/group. *** $P<0.001$ compared with VEH/VEH; $^{+++}$ $P<0.001$ compared with MEPH/VEH.

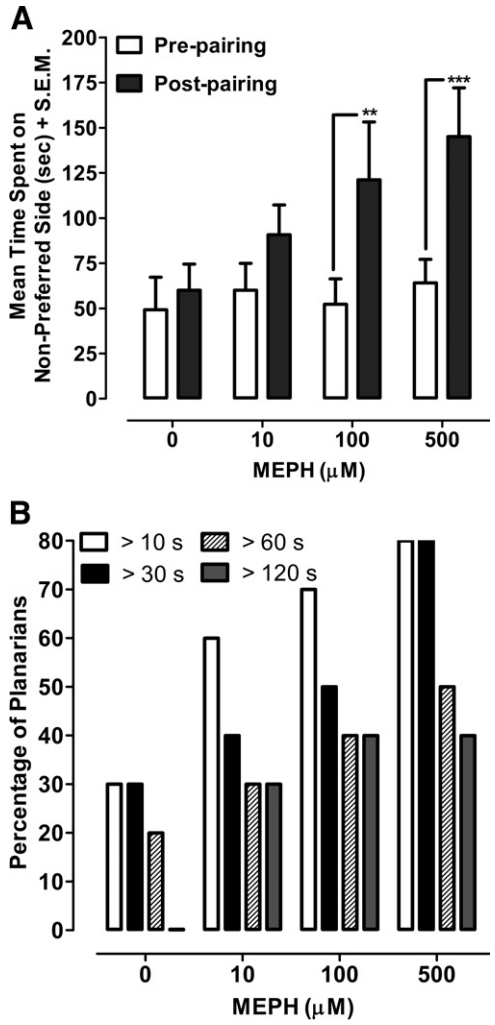


**Fig. 3.** Mephedrone (MEPH) (0, 10, 100, 500 $\mu$M) conditioning elicits a shift in environmental preference. (A) Data are presented as the mean time (s) (+SEM) spent on the non-preferred side before mephedrone conditioning (pre-pairing) and after mephedrone conditioning (post-pairing). $n=10$ planarians per group. * $P<0.05$, ** $P<0.01$ compared with pre-pairing response. (B) Data are presented as the percentage of planarians displaying a shift in preference between pre- and post-paring of greater than 10, 30, 60, and 120 s $n=10$ planarians/group.

have been described as "seizure-like activity" on the basis of evidence that proconvulsants induce stereotyped movements that are prevented by concurrent exposure to antiepileptic agents (Rawls et al., 2009; Ramakrishnan and Desaer, 2011). Furthermore, planarians exposed to cholinergic agonists exhibit muscle contractions that resemble stereotyped movements (Nishimura et al., 2010). Given reports that mephedrone induces toxicity in humans (Winstock et al., 2010), it cannot be discounted that the stereotyped movements observed here were partly because of a proconvulsant action of mephedrone. It is interesting to note that stereotyped movements elicited by cocaine and nicotine exhibit a concentration-related trend similar to mephedrone (Rawls et al., 2010b, 2011), and that high doses of cocaine and nicotine produce seizures in rodents (Zagnoni and Albano, 2002).

A pharmacological marker of acute psychostimulant activity in rodents and planarians is enhanced dopaminergic transmission (Creese and Iversen, 1974; Ujike et al., 1989; Algeri et al., 1983; Palladini et al., 1996). Recent studies indicate that mephedrone causes hyperactivity in rats at doses that also elevate extracellular dopamine in the nucleus accumbens (Hadlock et al., 2011; Martínez-Clemente et al., 2012). In the present experiments, a dopamine receptor antagonist (SCH 23390) inhibited a significant proportion of mephedrone-induced stereotyped movements in planarians, thus linking the motor-activating properties of mephedrone to an increase in dopamine signaling. The present finding is consistent with the postulated mechanism of action of mephedrone as an indirect dopamine agonist that enhances motor activity through a dopamine reuptake block (Kehr et al., 2011; Hadlock et al., 2011). The efficacy of SCH 23390 in planarians was dependent on its time of administration. In the case in which SCH 23390 was administered as a pretreatment, a robust inhibition of mephedrone-evoked stereotyped movements was detected. SCH 23390 was less efficacious in the case in which it was simply co-administered with mephedrone. One explanation for the time-dependent effects is that the component of dopamine signaling inhibited by SCH 23390 plays a greater role in the development, rather than expression and maintenance, of mephedrone-induced stereotyped movements. Regardless of the timing of administration, SCH 23390, a dopamine $D_1$ receptor antagonist (Hyttel, 1983), did not produce a complete block of the mephedrone effect. The lack of a complete block by SCH 23390 suggests that mephedrone acted through more than one mechanism, such as activation of multiple dopamine receptor subtypes or modulation of non-dopaminergic neurotransmitter systems, to produce stereotyped movements in planarians. Future studies will better define the possible mechanism(s) underlying acute behavioral effects of mephedrone.

Although rats and mice display increases in locomotor activity following acute exposure to psychostimulant drugs, including mephedrone (Kehr et al., 2011), planarians did not exhibit increases in motility following acute exposure to mephedrone. In fact, compared to vehicle-treated controls, higher concentrations of mephedrone (e.g. $\geq$500 $\mu$M) actually reduced motility, whereas lower concentrations produced no effect. The present finding with mephedrone is not an unexpected result given that more established stimulants, including nicotine, cocaine, amphetamine, methamphetamine, and caffeine, do not consistently enhance planarian motility following acute exposure (Rawls et al., 2010a,b, 2011; Pagán et al., 2008; Sacavage et al., 2008; Raffa et al., 2008). In the case of nicotine, the lowest concentration tested (10 $\mu$M) produced a slight increase in motility, whereas higher concentrations that elicited the most robust increases in stereotyped movements inhibited motility (Rawls et al., 2011). A similar profile was observed for mephedrone in the present study. It is not entirely clear why increases in planarian motility are not routinely de-

tected following acute exposure to psychostimulant drugs, but one reason may be because of limitations in methodology, rather than to specific physiological differences between planarians and rodents. For example, we have speculated that planarians are moving at maximum speed in the petri dishes, thereby resulting in a natural ceiling effect that masks potential increases in motility that may occur during acute exposure to a stimulant. This phenomenon may also explain why decreases in planarian motility are often observed following pharmacological manipulations. Another consideration is that rodents, before administration of drugs, are allowed to acclimate to their test cage environments to enable stabilization of baseline activity. Utilization of a comparable acclimation interval in naturally aquatic planarians is methodologically impractical because drug administration is accomplished through placement of planarians into a drug-containing solution rather than by injection. Thus, despite evidence that psychostimulant drugs elicit a number of parallel responses in planarian and rodent assays, including a withdrawal response following cessation of exposure, an environmental preference shift following conditioning, behavioral sensitization following repeated exposure, and stereotyped movements following acute exposure (Raffa and Rawls, 2008), the nature of the motility response is apparently different.

A withdrawal response was detected following spontaneous discontinuation of mephedrone exposure. The response was decreased motility, an effect also detected during abstinence from cocaine, amphetamines, nicotine, benzodiazepines, and opioids (Raffa et al., 2008; Raffa and Rawls, 2008). Planarian motility was reduced only during the condition of mephedrone abstinence and not during acute or continuous mephedrone exposure. Furthermore, prior work indicates that planarian motility is not reduced following discontinuation of exposure to “control” drugs that lack abuse liability, such as opioid antagonists, glutamate receptor antagonists, and nitric oxide synthase inhibitors (Rawls et al., 2007). Because a withdrawal response that is evident only during drug abstinence is a distinguishing feature of physical dependence, the present results suggest that planarians developed physical dependence to mephedrone. Human reports suggest that more frequent mephedrone use is associated with greater consumption, a finding that is consistent with the development of tolerance and dependence (Newcombe, 2009). Another possibility is that the reduction in planarian motility during mephedrone abstinence reflected a “depressive-like state” caused by catecholamine depletion, similar to the immobility that psychostimulant withdrawn rats display in the forced swim assay (Chae et al., 2008). Although decreased motility was the only overt planarian withdrawal response detected in our experiments, it can be predicted that higher mephedrone concentrations would elicit a more intense withdrawal syndrome consisting of a broader spectrum of responses. For example, in the case of nicotine, the withdrawal syndrome is concentration sensitive, with low concentrations causing reduced motility and higher concentrations causing reduced motility and higher concentrations causing stereotypical behaviors including headbops, headswings, tailtwists, and corkscrews (Raffa and Desai, 2005; Pagán et al., 2009; Rawls et al., 2011).

Mephedrone elicited a conditioned place preference in planarians. To enable the environment (dark or ambient light) to act as a conditioned stimulus, the non-preferred environment was determined before mephedrone exposure and then paired with the subjective effects of mephedrone. Planarians then prefer, or avoid, the conditioned environmental stimulus depending on the rewarding or aversive properties of the paired substance (mephedrone in this case). Experiments revealed that planarians conditioned with mephedrone, but not vehicle, displayed a concentration-related shift in environmental preference, that is, they preferred the environment paired with mephedrone, even though that is contrary to their natural preference. Thus, mephedrone appears to have reward properties. For example, in planarians conditioned with the highest concentration (500 $\mu$M), 80% displayed preference shifts of greater than 30 s, 50% displayed a shift of greater than 60 s, and 40% displayed a shift of more than 120 s. In contrast, only 30% of mephedrone-naive planarians displayed a shift of greater than 30 s, and none displayed a shift greater than 120 s. The present data suggest that subjective properties of mephedrone can be associated with environmental cues and essential pathways that mediate the pharmacological effects of addictive substances are conserved. More experiments are required to determine if the conditioned place preference demonstrated for mephedrone in planarians translates to mammals, but it is known that two psychoactive drugs, methamphetamine and nicotine, cause environmental place conditioning in planarians (Kusayama and Watanabe, 2000; Rawls et al., 2011).

## CONCLUSIONS

Mephedrone elicited three psychostimulant-like behavioral effects that are consistent with a psychostimulant-like mechanism of action: a dopamine-sensitive increase in stereotypical activity, an abstinence-induced withdrawal response, and a conditioned place preference. Together with recent neuropharmacological data from rats (Kehr et al., 2011; Hadlock et al., 2011; Martínez-Clemente et al., 2012), the present behavioral data suggest that pharmacological responses to mephedrone are conserved across different species, provide further clues about the pharmacological profile of mephedrone, and provide evidence that the compound likely possesses abuse potential that is consistent with psychostimulant drugs.

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