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Neurobehavioural Effects of Acute and Repeated Administrations of Sub-Psychotomimetic Dose of Ketamine in Mice

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Abstract

Recent studies have shown that sub-anaesthetic doses of ketamine may induce analgesia, but its psychotomimetic side effects have called for caution. This study therefore, explored a possible sub-psychotomimetic dose of ketamine (SPDK) and determined the influence of frequency of exposure on its neurobehavioural effects in mice. Mice of either sex weighing 18 - 25 g were randomly selected into three major groups: A, B, and C. Group A was distributed into seven sub-groups (n=12) and treated with saline (10 µL/g/body weight); 1, 2, 4, 6, 8, and 10 mg/kg ketamine for stereotyped horizontal locomotion (SHL) assessment using the open field test. Groups B and C were each allotted into three sub-groups (n=7): I, II, and III. They were treated with saline (10 µL/g/body weight) as negative control, 1 mg/kg ketamine and 1.5 mg/kg scopolamine as positive control; and assessed for neurobehavioural effects of acute and repeated administrations using elevated plus-maze (EPM) and Y-maze respectively. Data were presented as Mean ± SEM and analyzed using ANOVA followed by Student-Newman-Keuls test with $p < 0.05$. The results showed that 1 mg/kg ketamine is devoid of psychotomimetic side effects (1.979, $p > 0.05$), whereas, ketamine 2, 4, 6, 8 and 10 mg/kg induced significant increase (8.258, $p < 0.001$), (7.688, $p < 0.001$), (7.916, $p < 0.001$), (10.580, $p < 0.001$) and (13.244, $p < 0.001$) respectively in SHL compared with the saline group in the open field paradigm. Therefore, ketamine 1 mg/kg was chosen as the sub-psychotomimetic dose. Acute administration of SPDK did not significantly impair memory of mice in both EPM (6.751, $p < 0.001$) and Y-maze models (3.467, $p < 0.05$), whereas, its repeated administrations showed comparable results to the group administered scopolamine in both EPM (0.1460, $p > 0.8654$) and Y-maze models (1.258, $p > 0.3126$). This study concluded that 1 mg/kg of ketamine may be a sub-psychotomimetic dose; and ketamine-induced psychotomimetic side effects and cognitive impairments could be dose and time-dependent respectively.

***Keywords*:** Neurobehavioural effects; sub-psychotomimetic dose of ketamine; drug re-positioning; stereotyped horizontal locomotion; scopolamine

Introduction

The search to develop novel drugs that are more effective and less toxic compared to the existing ones as alternative therapies is intense (Amaral *et al.*, 2007). Unfortunately, the process of drug discovery and development is faced with innovations, legal and financial challenges (Vogel., 2002 and Morgan *et al*, 2017) which has necessitated the need for the pharmaceutical industry to adopt the concept of drug 're-positioning' or 'repurposing' (Katare *et al*., 2016). This approach is the use of an existing drug for newly discovered therapeutic purpose(s) other than the original indication or the usual therapeutic use(s) (Dudley *et al*., 2011) or identification of novel indication(s) for an existing drug(s) rather than searching for a new active pharmaceutical ingredient (API) (Boshu *et al*., 2017). The approach reduces the time and attendant huge cost of developing a new drug (Pandeya and Dimmock, 2012; Cooper, 2017).

Ketamine is incredibly unique for its dexterous ability to provide anxiolysis, analgesia, and amnesia simultaneously (McCarthy *et al.*, 2013). Historically, its profound analgesic activity at higher doses was observed at the developmental stage (Aroni *et al.*, 2009), yet was not really explored probably due to its hallucinogenic, cognitive impairment (Moghaddam *et al.*, 1997), and psychotomimetic side effects. However, the involvement of NMDA receptors in the processing of nociception (Woolf and Thomson, 1991), and the report of low-dose ketamine to induce analgesia (Arbabi and Ghazi-Saeidi, 2003; Bell, 2009; Borsook, 2009, Bell and Moore, 2010), have led naturally to renewed clinical interest in ketamine (Owolabi *et al*., 2018), yet its psychotomimetic side effects have limited its otherwise numerous clinical applications.

Studies have shown that higher doses of non-competitive NMDA receptor antagonists including phencyclidine (PCP) cause schizophrenic-like effects in both human and rodents (Krystal *et al*., 1994 and Malhotra *et al*., 1996, 1997). In fact, sub-anaethetic doses of ketamine have been implicated in psychosis and memory dysfunction in animals (Krystal *et al*., 1994; Pitsikas *et al*., 2008 and de Oliveira *et al*., 2009). Meanwhile, few preclinical and clinical studies have been able to report doses of ketamine that are devoid of psychotomimetic effects (Sens *et al*., 2005; Lopez, 2007; and Yezierski, 2012). Such results are inconsistent and in fact contradictory. This study was therefore designed to explore the possible dose of ketamine that would be devoid of psychotomimetic side effects and cognitive impairment following acute and repeated administrations in mice. This is with a view to determining whether the psychotomimetic side effect and ketamine-induced cognitive impairment are dose- and/or time-dependent or otherwise, thus, providing explanation to promoting the re-positioning of ketamine as an anti-nociceptive agent.

Materials and Methods

Animals

Swiss albino mice of either sex weighing 18-25 g were used for this study. They were obtained from the animal house of the Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, (O. A. U.) Ile-Ife, Nigeria. This was followed by random distribution into different groups of six-members each. They were housed in standard animal cages and had access to food and water *ad libitum*. Guidelines applying to animal use and experimental procedures as stipulated and approved (PHP12/13/H/0607) by the Research Ethics Committee of O. A. U. Postgraduate College were duly observed. All experimental procedures were conducted between 8 a.m. and 6 p.m.

Drugs and Reagents

Ketamine hydrochloride (50 mg/ml, Rotex Medica Trittau, Germany), scopolamine 1.5 mg/kg (Sigma, St. Louis, MO, USA), normal saline (10 µL/g/body weight, Drugfield Pharmaceuticals Ltd, Nigeria), methylated spirit (Royal Priesthood Lab. Ltd, Nigeria), and distilled water (Pharmacology Lab, O. A. U., Ile-Ife) were used. All reagents and drugs were appropriately kept in manufacturers' recommended storage conditions.

Apparatus and Materials

Open field box (OFB), elevated plus maze (EPM), Y-maze, stopwatch, electronic weighing balance (Golden-Mettler, U.S.A.), counter machine (H20Link, Germany), and consumables were the materials used.

Experimental Procedures

Assessment of Sub-Anaesthetic Doses of Ketamine on Stereotyped Horizontal Locomotion Using Open Field Test

Eighty-four mice were used in this procedure to determine sub-psychotomimetic dose of ketamine. They were randomly distributed into 7 groups (n = 12). All animals were allowed 60 minutes to acclimatize to the observation cage before the administration of ketamine (Ellerma *et al*., 2002). Group 1 received 10 µL/g/body weight i.p. normal saline as control, while other groups: 2, 3, 4, 5, 6, and 7 were administered 1, 2, 4, 6, 8, and 10 mg/kg i.p. ketamine respectively. After 5 minutes post-administration of ketamine, each mouse was observed and scored for stereotyped locomotion using the square method according to the modified scale of Stugeron *et al.,* (1979) and Hoffman (1992) during 30 seconds of every 5 minutes for a period of 60 minutes (Owolabi *et al*., 2008).

Locomotion was scored as follows: 0 = stationary, 1 = movement within a given square, forelimbs, 2 = intermittent movement within half of the area of the cage, 3 = continuous movement within half of the area of the cage, 4 = intermittent movement within the whole area of the cage, 5 = continuous movement within the whole area of the cage. The apparatus was cleaned with methylated spirit and

allowed to dry in-between sessions in order to remove the odour of previous animals (Bamitale *et al*., 2011)..

Assessment of Neurocognitive Effects of Acute and Repeated Administrations of Sub-psychotomimetic Dose of Ketamine Using Elevated Plus-Maze Model

Twenty one mice which were divided into 3 groups (n = 7) were used in this procedure. Each mouse was allowed to explore the maze for 5 minutes and then returned to its home-cage on the first day (learning session). Twenty-four hours after the first day trial, groups 1, 2, and 3 received 10 μL/g/body weight normal saline (negative control), 1 mg/kg ketamine i.p. (acute administration), and 1.5 mg/kg scopolamine (positive control), respectively. After five minutes post-treatment, each mouse was placed at the end of an open arm, facing away from the central platform on the elevated plus-maze (Ishola *et al*., 2013) to score the duration of transfer latency which is defined as the time (in seconds) taken by the mouse to move from the open arm into one of the closed arms with all its four limbs (Joshi and Parle, 2006). Thereafter, the animals were crossed over to repeated administrations of the drugs and saline to respective groups once daily for 21 days and were again exposed to the elevated plus-maze 5 minutes post-treatment on the 21st day. The apparatus was wiped with cotton swab after each session to remove the odour of the previous animal.

Assessment of Neurocognitive Effects of Acute and Repeated Administrations of Sub-psychotomimetic Dose of Ketamine Using Y-Maze Model

Another set of twenty one mice were distributed into 3 groups (n = 7) and used in this procedure. Each mouse was allowed to explore the maze for 5 minutes and then returned to its home-cage on the first day (learning session). Twenty-four hours after the first day trial, groups 1, 2, and 3 received 10 μL/g/body weight normal saline (negative control), 1 mg/kg ketamine i.p. (acute administration), and 1.5 mg/kg scopolamine (positive control), respectively. After 5 minutes of drug treatment, each mouse was placed in one of the arm compartments and allowed to move freely for 6 minutes without rein forcers. Examined parameters were: total arm entries and spontaneous alternation. An arm entry is when the body of a mouse, except for its tail, completely entered into an arm compartment while spontaneous alternation percentage (spatial working memory)was defined as an entry into all three arms on consecutive choices (Akanmu *et al.*, 2011). The sequence of arm entries, which are alternations, was mutually recorded and the number of maximum spontaneous alternations was therefore the total number of arms entered minus 2, and the percentage spontaneous alternation (% SA) was calculated as thus:

$$\frac{\text{Actual alternations}}{\text{Maximum alternations}} \times 100$$

Thereafter, the animals were crossed over to repeated administrations of the drugs and saline to respective groups once daily for 21 days and were again exposed to the Y-maze 5 minutes post-treatment on the 21st day.

Data Analysis

Data were expressed as Mean ± SEM. The results were evaluated using One-way Analysis of Variance (ANOVA), followed by post-hoc tests (Student- Newman-Keuls Test). $^{*}P$ <0.05 was considered as accepted level of significant difference from the controls. GraphPad Instat® Biostatistics software (GraphPad Software Inc., La Jolla, U.S.A.) were used for computer data analysis.

Results

Assessment of stereotyped horizontal locomotion in mice with sub-anaesthetic doses of ketamine using Open Field Test.

One-way ANOVA showed significant differences in stereotyped horizontal locomotion across all the groups ($F_{(6, 77)}$= 21.475, p< 0.0001). However, Post-hoc analysis revealed that there was no significant difference in stereotyped horizontal locomotion between saline and 1 mg/kg ketamine group ($F_{(6, 77)}$= 1.979, p> 0.05) whereas, there were statistical differences between stereotyped locomotion of all other treated groups when respectively compared with saline group. Therefore, 1 mg/kg ketamine was considered as the sub-psychotomimetic dose among the sub-anaesthetic doses of ketamine considered in this study as shown in Figure 1 below.

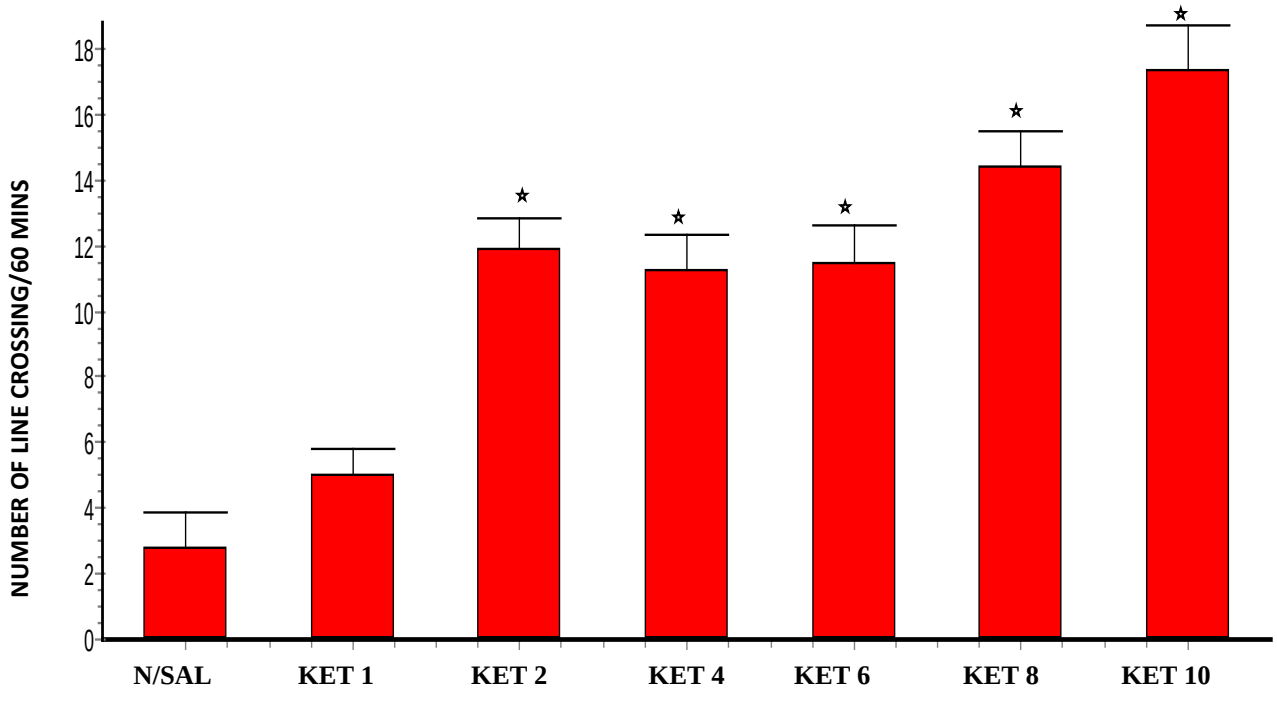

Figure 1: Assessment of stereotyped horizontal locomotion in mice with sub-anaesthetic doses of ketamine using Open Field Test. The columns and vertical bars represent Mean and SEM respectively, (n = 12), **P*< 0.05 relative to saline group.
N/SAL= Normal Saline 10 µL/g/body weight, KET 1, KET 2, KET 4, KET 6, KET 8, and KET 10 = ketamine 1, 2, 4, 6, 8, and 10 mg/kg respectively.

Neurocognitive Effects of Acute and Repeated Administrations of 1 mg/kg Ketamine on the Performances of Mice in the Transfer Latency Behavioural Test Using Elevated Plus-Maze

One-way ANOVA revealed statistical differences ($F_{(2, 18)} = 15.476$, $p < 0.0001$) in the transfer latencies of all groups of mice that were given either the acute administrations of the test drug or the controls. Post-hoc analysis however showed significant transfer latencies in groups of mice acutely administered saline (6.875, $p < 0.001$) and ketamine 1 mg/kg (6.751, $p < 0.001$) when respectively compared to the group administered scopolamine alone as shown in Figure 2, whereas, no statistical difference was recorded between the groups that were acutely administered saline and ketamine 1 mg/kg. Meanwhile, one-way ANOVA showed no difference in transfer latencies ($F_{(2, 17)} = 0.1460$, $p > 0.8654$) across groups that were repeatedly administered either the test drug or controls as revealed in Figure 3.

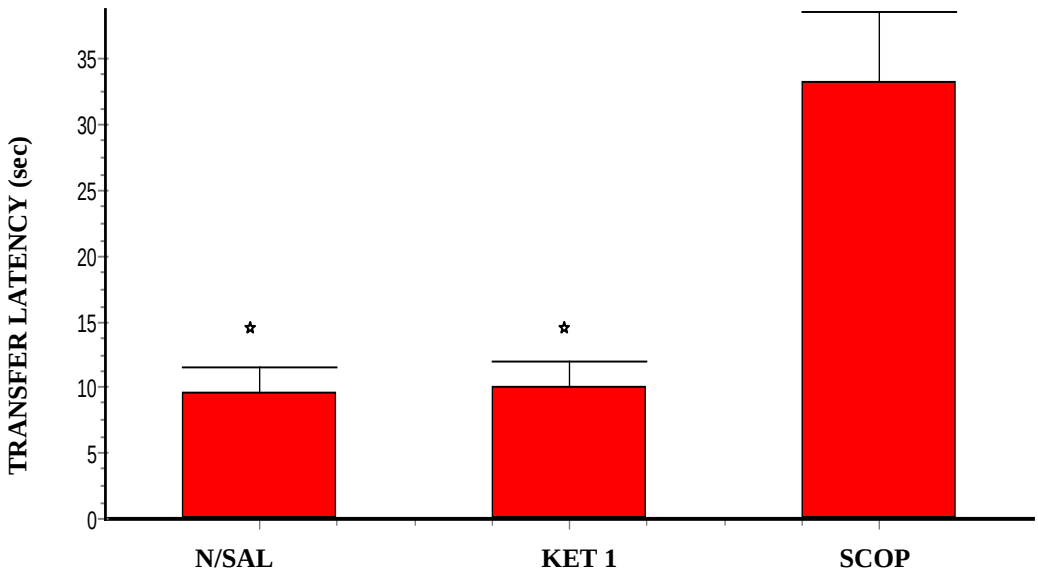

Figure 2: Assessment of neurocognitive effect of acute administration of 1 mg/kg ketamine using elevated plus-maze model**.** The columns and vertical bars represent Mean and SEM respectively, (n = 7), *p< 0.05 relative to scopolamine group. N/SAL= Normal saline 10 µL/g/body weight, KET 1 = ketamine 1 mg/kg, SCOP = Scopolamine 1.5 mg/kg

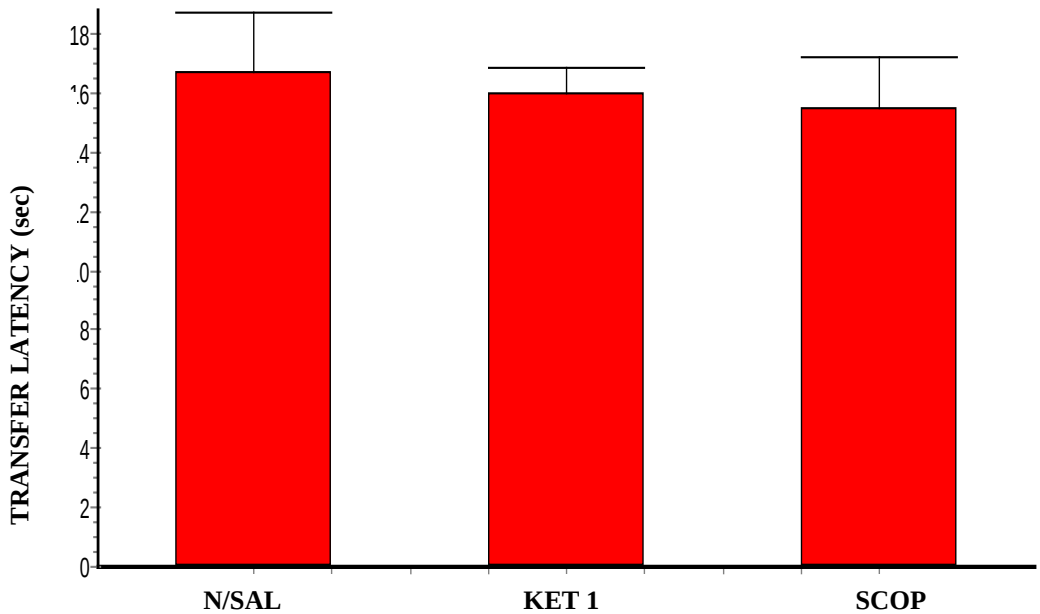

Figure 3: Assessment of neurocognitive effect of repeated administrations of 1 mg/kg ketamine using elevated plus-maze model**.** The columns and vertical bars represent Mean and SEM respectively, (n = 5 - 7). N/SAL= Normal saline 10 µL/g/body weight, KET 1 = ketamine 1 mg/kg, SCOP = Scopolamine 1.5 mg/kg

Neurocognitive Effects of Acute and Repeated Administrations of 1 mg/kg Ketamine on the Performances of Mice in the Spontaneous Alternation Behavioural Test Using Y-Maze

One-way ANOVA revealed statistical differences ($F_{(2, 18)} = 6.628$, $p < 0.0070$) in the percentage spontaneous alternations on mice across groups that were given acute administrations of either test drug or the controls. Post-hoc analysis however showed that percentage spontaneous alternations were significantly different in the groups acutely administered ketamine 1 mg/kg (3.467, $p < 0.05$) and saline (5.030, $p < 0.01$) when compared to the scopolamine group as shown in Figure 4. Nonetheless, difference was not observed between the groups that were given acute administrations of saline and ketamine 1 mg/kg. Meanwhile, one-way ANOVA showed no difference in percentage spontaneous alternations ($F_{(2, 17)}=1.258, p>0.3126$) across groups that were repeatedly administered either the test drug or controls as depicted in Figure 5.

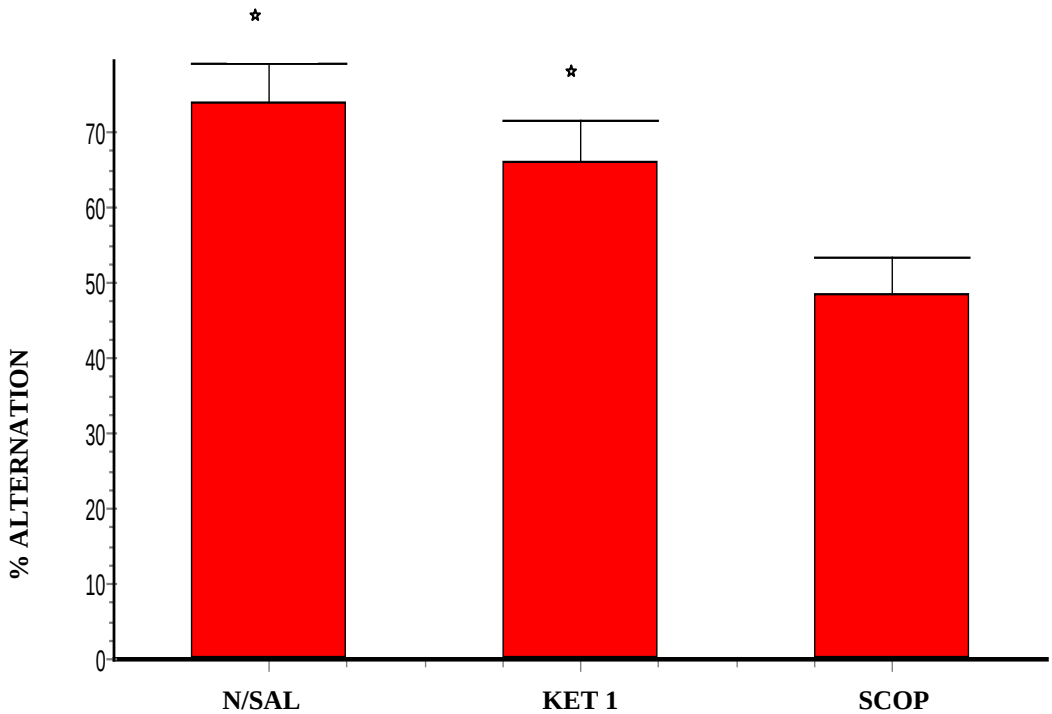

Figure 4: Assessment of neurocognitive effect of acute administration of 1 mg/kg ketamine using Y-maze model**.** The columns and vertical bars represent Mean and SEM respectively, (n = 7), *p< 0.05 relative to scopolamine group. N/SAL= Normal saline 10 µL/g/body weight, KET 1 = ketamine 1 mg/kg, SCOP = Scopolamine 1.5 mg/kg

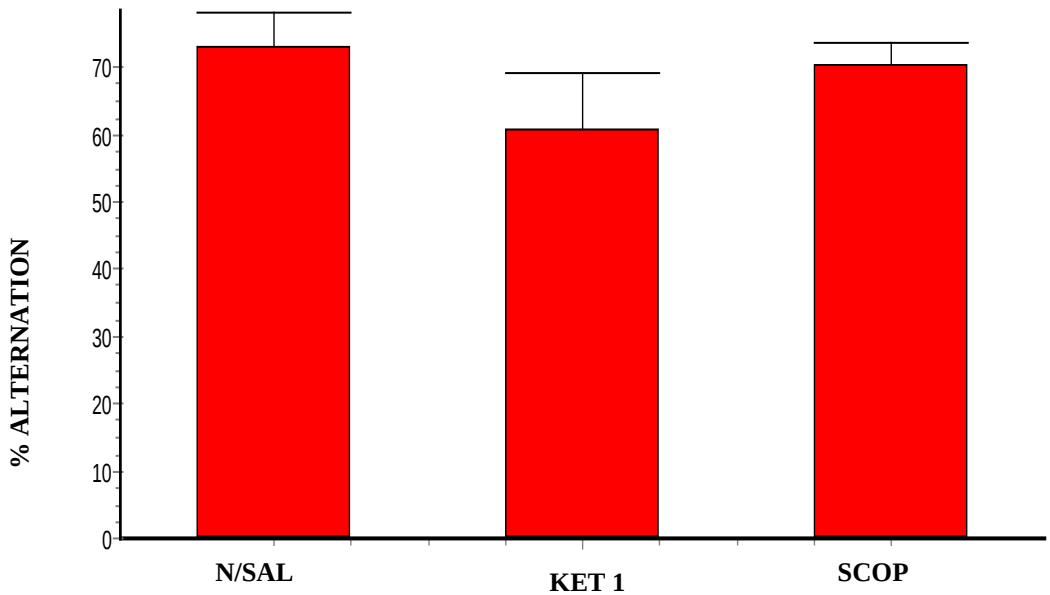

Figure 5: Assessment of neurocognitive effect of repeated administrations of 1 mg/kg ketamine using Y-maze model**.** The columns and vertical bars represent Mean and SEM respectively, (n = 5 - 7). N/SAL= Normal saline 10 µL/g/body weight,
KET 1 = ketamine 1 mg/kg, SCOP = Scopolamine 1.5 mg/kg.

Discussion and Conclusion

This study explored possible sub-psychotomimetic dose of ketamine using the open field paradigm and assessed the neurocognitive effects of its acute and repeated administrations using Elevated Plus-Maze and Y-maze models in mice. The Open Field Paradigm is a model used to assess the locomotor behaviour and exploratory activity of compounds (David *et al.,* 2016). Previous studies have validated the use of stereotyped locomotion in the open field box as a model for the assessment of psychotomimetic effects of psychoactive substances (Stugeron *et al.,* 1979 and Hoffman, 1992) and specifically for ketamine (Ellerma *et al*., 2002). Among the sub-anaesthetic doses (1, 2, 4, 6, 8 and 10 mg/kg) of ketamine evaluated in this study, it was observed that only 1 mg/kg of ketamine did not significantly increase stereotyped behaviour in mice relative to the saline group whereas, ketamine 2, 4, 6, 8 and 10mg/kg respectively induced significant increase in stereotyped horizontal locomotion when compared with the saline group in the open field paradigm. This suggests that ketamine 1 mg/kg may be devoid of psychotomimetic side effects.

The elevated plus-maze is a modification of the apparatus originally developed by Pellow *et al.,* (1985) which was validated for measuring anxiety in mice (Lister, 1987). It is well known to serve as the exteroceptive behavioral model to evaluate memory in mice (Ishola *et al*., 2013 and 2017) whereby significant reduction in transfer latency value of retention indicates memory improvement (Joshi and Parle, 2006). Naïve mice will normally prefer to spend less time in the open arm rather than the closed arm (Rodgers and Cole, 1994) which gives a safe haven and thus the mouse spends much time therein (open arm). Similarly, Y-maze model has been reported to be useful in assessing short-term memory, general locomotor activity and stereotypic behaviour (Kokkinidis *et al*., 1976). It is well known that spontaneous alternation performance which is defined as an entry into all three arms on consecutive choices is a measure of spatial working memory (Sarter *et al.,* 1988; Heo *et al*., 2003; Mamiya *et al*., 2004). Scopolamine, also called hyoscine or levo-duboisine, is a tropane alkaloid drug with muscarinic anti-cholinergic effects. It acts competitively as an antagonist specifically on the M_1acetylcholine receptor. Scopolamine causes memory impairments (Bartus *et al*., 1982) in healthy young humans that paralleled the impairments of memory seen in non-demented drug free elderly (Klinkenberg and Blokland, 2010) thus, was used as a standard in this study.

Since previous studies have shown that sub-anaesthetic doses of ketamine could impair Some domains of cognitive functions, such as attention, free recall, recognition memory and thought processes in healthy human volunteers (Krystal *et al*., 1994, 2003; and Malhotra *et al*., 1996), and that NMDA pathways have been implicated in disorders like psychosis, and memory dysfunction (Lahti et al., 1995; Malhotra *et al*., 1997; Wolf, 1998; Krystal *et al*., 1995, 2005; Eva and Michael, 2002). There is a possible neurocognitive effects of the SPDK were thus evaluated using EPM and Y-maze models. Our study showed that acute administration of 1 mg/kg ketamine did not impair cognitive functions in mice

in both EPM and Y-maze models. Contrarily, the repeated administrations showed comparable results to the scopolamine groups in both EPM and Y-maze models thereby suggesting that repeated exposure to ketamine (even at sub-psychotomimetic dose) induces memory impairment in mice. The non-induction of memory impairment of acute administrations of SPDK may however be explained by the fact that ketamine is a short-acting agent whereas its repeated administrations could have induced functional hypersensitivity to NMDA receptors (Owolabi and Akanmu, 2014), thereby causing memory impairment (Lindefors *et al*., 1997) in mice.

It can thus be inferred that the memory impairment induced by ketamine is time and dose-dependent and that repeated exposure to ketamine may cause cognitive dysfunction similar to the phencyclidine (Stugeron *et al.,* 1979 and Owolabi *et al*., 2008). Hence, the result obtained corroborated previous findings that sub-chronic administration of ketamine induced memory damage in animals (Moghaddams *et al*., 1997 and Celia, 2004). It is however recommended that further studies to assess the analgesic effect of sub-psychotomimetic dose of ketamine be conducted in animals.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgments

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