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ORIGINAL ARTICLE

Memory deficits associated with khat (*Catha edulis*) use in rodents

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Abstract Khat products and chewing practices are common in East Africa, Middle East for centuries with concomitant socio-economic and public health repercussions. We assessed memory deficits associated with khat use in rodents. Young male CBA mice, 5–7 weeks old ($n=20$), weighing 25–35 g were used. Mice were treated with either 40, 120 or 360 mg/kg body weight (bw) methanolic khat extract, or 0.5 ml saline for 10 days. Spatial acquisition, reversal and reference memory were assessed using modified Morris Water maze (MMWM). Mice treated with 40 mg/kg khat extract had longer ($t_4=4.12$ $p=0.015$) and $t_4=2.28$ $p=0.065$) escape latency on first and second day during reversal relative to the baseline. Under 120 mg/kg khat dose, the escape latency was shorter ($t_4= -2.49$ $p=0.05$) vs ($t_3=-2.5$ $p=0.05$) on third and fourth day. Further, treatment with 360 mg/kg khat extract resulted in significantly longer time (49.13, 33.5, 40.2 and 35.75) vs. (23.5 s), compared to baseline. Mice treated with khat or control preferred the target quadrant post acquisition while differential pattern was seen during reversal phase. Mice treated with 40 or 120 mg/kg khat showed significant preference for target quadrant. Substantial time (19.9) was spent in the old target compared to the new (16.9 s) by animals treated with highest dose however, the difference was not significant. There is a biological plausibility that chronic khat use may induce memory deficits and impair cognitive flexibility. The differential patterns of memory deficits may reflect the differences in dose effect as well as time dependent impairment.

Keywords Khat · Reference memory · Cognitive inflexibility · Acquisition learning · Reversal learning

Introduction

Plant products have been used for food, medicinal, and mind alteration since the first generation of mankind. Khat (*Catha edulis*) is a plant whose products have psycho-stimulant effects. The plant has been grown and utilized for centuries among people living in the horn of Africa, East Africa and the Middle East (Gebissa 2010; Carlini 2003; Connor et al. 2002) for the "feel good" (psycho-stimulant) effects. Technological advancement in transport, notably refrigerated air transport has facilitated its availability and access to many people and/or parts of the world (Al-Motarreb et al. 2002) resulting in globalization of khat use practices. Furthermore, emigration of people from traditional khat chewing countries while running away from armed conflicts, civil strife, lawlessness, terrorism, seeking asylum in North America, Australia and European, have facilitated the spread of the practice (Sheikh 2014). Export of khat products and chewing practices have been accompanied by concomitant transfer of the associated socio-economic and health problems. Among the salient problems associated with khat include daily use with resultant compulsive and psychic dependence on the drug (Eddy et al. 1965), public health, medical, economic and social repercussions (Al-Motarreb et al. 2010).

Fresh khat is preferred and whereas it contains many ingredients, cathinone is the main alkaloid. Cathinone has structural similarity to amphetamine and is mainly responsible for most of psychoactive properties of khat (Kalix 1992; United

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Nations 1975; Szendrei 1980). Like amphetamine, cathinone acts by releasing catecholamines from pre-synaptic storage sites, inhibiting their re-uptake, thereby increasing their temporal and spatial presence at the pre-synaptic receptors (Kirkyby 1969; Safer and Krager 1998). Cathinone has also been associated directly or indirectly with dopamine or serotonin release via action on their transporter functions (Banjaw et al. 2003). Additionally, cathinone releases dopamine which acts through D_1 type receptors to modulate its reinforcing effects (Kalix 1990). The neurotransmitter systems through which cathinone (khat) modulates its mechanistic processes appears to be important pathways for neurobehavioral activities including learning and memory (Hoffman and Absi 2010).

Khat use has been implicated with acute as well as chronic physio-neuro-psychological and mental outcomes (Zelger et al. 1980; Brenneisen et al. 1990). Khat has been used to prevent fatigue, improve concentration and flow of ideas when studying (Balint et al. 2009; Gray and Roth 2007; Kalix 1992) and perceived believe of improving memory (Mohammed et al. 2014, 2015). These findings have been corroborated by studies that showed improvement on spatial learning and memory in rodents following khat extract administration (Kimani and Nyongesa 2008). Additionally, chronic khat use has been implicated with impaired working memory and mental impairments (Colzato et al. 2011; Hoffman and al'Absi 2013). Although evidence from both human and animal studies have demonstrated acute and chronic khat's neuro-behavioural effects, there is limited information on its effect on reversal learning and memory. We therefore sought to investigate memory deficits associated with khat (*Catha edulis*) use in rodents.

Materials and methods

Experiments on elucidating the differential patterns of cognitive deficits associated with khat in rodents was conducted in the department of medical physiology, University of Nairobi, Kenya.

Chemicals

Methanol (CAS No. 67-56-1, 99 % purity) was bought from Sigma–Aldrich (St. Louis, MO) and stored at room temperature. All other laboratory reagents were of analytical or molecular biology grades.

Animals

Young adult CBA male black mice, 5–7 weeks old ($N=20$), weighing 25–35 g upon arrival were used. The mice were acquired from the Department of Medical physiology, University of Nairobi. These mice are commonly bred, used and have also been extensively utilized in neurobiology of learning and memory (Nguyen et al. 2000; Nguyen 2007). The animals were housed in plastic cages ($30\times15\times12$ cm) in groups of five. The beddings were made of wood shavings and changed every 2 days. Mice were used as per institutional regulations on colony handling and efficient use of laboratory animals.

Diet

A normal rodent pellet diet was purchased from Unga Feeds (Nairobi, Kenya). This was commercially available diet for mice with all the necessary vitamins and minerals. Animals were fed and given tap water ad libitum for 4 weeks during acclimatization and treatment phases.

Preparation of khat extract

Bundles of fresh khat were obtained from Westlands market, Nairobi Kenya. The khat leaves and shoots were weighed (140.96 g), crushed with pestle and mortar and thereafter mixed with 1500 ml of methanol. The mixture was gently stirred and left to stand overnight. The mixer was filtered with cotton gauze to remove large particles while, the resultant material was filtered with Whatman No. 1 filter paper. Methanol was removed by evaporating the mixer using a Rotavac control evaporator (Heidolph, Germany) set at 65 °C, 100 rpm and 240 Pascal negative pressure. The resultant extract weighed 60.30 g in a volume of 65.30 ml. The extract was used to prepare a working concentration of 923.4 mg/ml. The working concentration was used to prepare the extract dose regime of 40, 120 and 360 mg/kg body weight, respectively.

Dosing regimens

Mice were acclimated with handling and navigation within the water maze for a 5-day period. On the 6th, mice were assigned to experimental groups ($N=5$/group) and treated intraperitoneally (i.p) (one injection per day) for 17 days as follows: (1) 40 mg/kg body weight (bw) khat extract; (2) 120 mg/kg bw khat extract; (3) 360 mg/kg bw khat extract; (4) The control group ($n=5$) was administered with 0.5 ml normal saline i.p.

Animal observations

Mice were examined daily for physical signs of disease including skin, fur and changes in walking.

Water maze assessment

The performance of mice on learning and memory was assessed using a modified Morris water maze (MMWM). This behavioural paradigm has been used to assess hippocampal-dependent learning including acquisition as well as long-term spatial memory (Morris 1981; Bromley-Brits et al. 2011).

The MMWM consisted of black plastic circular tank (112 cm in diameter×25 cm depth). The tank was equipped with a white stable circular platform (11.5×18.5 cm) for use as an escape platform. The tank was filled with tap water up to a height of 19.5 cm. The water was warmed to 25 °C using an electric heater and monitored with a mercury thermometer. The white stable circular platform was submerged 1 cm below the water for mice to climb on it. To hide the escape platform, a non-toxic white paint (Xpress Color and Screen Ltd, Kenya) was added making the water white and providing good contrast against the black CBA mice.

The MMWM tank was arbitrarily divided into four quadrants namely North-West (NW), North-East (NE), South-East (SE), and South-West (SW). The boundaries of the quadrants were marked on the edges of the pool with a masking tape labeled North (N), South (S), East (E), and West (W). The tank was placed in an experimental room measuring 4.64×3.78 m fitted with distal visual cues placed on the walls.

The MMWM assessment was carried out in three phases namely spatial and reversal acquisition, and reference (long-term) memory. Mice were placed randomly in the maze at different starting positions while, the investigator maintaining the same position throughout the assessment procedure. The navigating mice in the MMWM were video-taped using a video camera (Type-Image video camera CAM) connected to a video camera recorder (VCP-C10, Toshiba PTE Ltd, Singapore), and a 14 in television (JVC Supermulti, Japan).

In the spatial acquisition phase, mice learn to use distal cues to navigate a direct path to the hidden platform when started from different, random locations around the perimeter of the tank (Vorhees and Williams 2006). Khat extract and/or normal saline were administered to the mice 30 min before daily sessions. The trial involved mice trying to locate the submerged platform placed in the center of SE (target) quadrant of the MMWM tank for 4 days. In each trial, mice were placed randomly at one of the start locations (N, S, W, and E) and allowed 60 s to search for the platform. Once the platform was located, the animals were allowed 30 s to stay on it. However, if 60 s elapsed and the mouse failed to locate the platform, the experimenter would guide and allow the animal 30 s stay on the platform so that it may develop its own navigation strategy (Morris 1981). At the end of each trial, the mouse was removed, dried with a paper towel and returned to the home cage awaiting the next trial.

The performance during each trial was determined using the following dependent variables; (i) escape latency, defined as time taken from the start position to the escape platform, measured with a stop-watch (Marathon Watch Company Ltd, China), (ii) swim distance, the swim path from start position to the platform, determined by replaying the video tape and tracing the mouse swim path with a marker pen on a tracing paper mounted on TV screen. Thereafter the swim path was determined using a map reader and the distance was corrected by multiplying with a factor of 5.65. This was the ratio of true maze diameter to the TV image, (iii) the swim speed was determined by dividing the swim distance and the escape latency.

The spatial reversal learning was also assessed. The assessment reveals whether or not animals can extinguish their initial learning of the platform's position and acquire a direct path to the new goal position (Vorhees and Williams 2006). The reversal learning assessment was carried out after (from day 6) acquisition phase. During the reversal training, the escape platform was moved to the NW quadrant directly opposite its location during acquisition phase. Mice were subjected to the training task with similar protocol as in the acquisition learning. The protocol involved four trials per day for 4 days, during which mice would locate the new location (quadrant) of the escape platform. The escape latency, swim path distance and swim speed were determined as described in the acquisition phase.

Reference (long-term) memory

The reference (long-term) memory phase was implemented through probe (transfer) trial. The probe trial was administered 24 h after the last acquisition day to determine reference memory independent of the acquisition memory or last training acquisition sessions (Vorhees and Williams 2006). Two probe trials were carried out; one after the acquisition (post acquisition probe trial) on day 5, while the second one, following the reversal memory assessment (post reversal learning probe trial) on day 9, respectively (Vorhees and Williams 2006). During the post acquisition probe trial, the escape platform was removed from SE quadrant and the MMWM did not have a platform. Each mouse was placed in the MMWM from N position the point directly opposite the location of the platform (SE) during acquisition phase for 60 s. On the other hand, the post reversal learning probe trial was carried with start position for each mouse being South (S) position. This was consistent with the fact that during reversal learning the escape platform was located in the NW quadrant. The time spent and the proportions of swim distance for each mouse in each quadrant were measured from the video recording as described above.

Statistical analysis

A simple linear regression for estimating the dependent variables during the last day of acquisition (baseline) were conducted to ensure that the treatment groups were not stating at different performance levels. The variables notably escape latency, swim path distance and swim speed for each trial were averaged into sessions and plotted as a means (± s.e.m.) per day for both acquisition and reversal learning. A paired *t*-test was carried out to compare the variables for each of the treatment group relative to controls. A paired *t*-test was also used to assess the influence of treatment on daily performance during reversal learning relative to the last acquisition day. In addition, during the probe trial mice performance in each of the quadrant were evaluated and compared using paired *t*-test. All statistical analyses we conducted at the significance level of p <0.05.

Results

Physical and behavioral observations

The experimental animals did not show any overt physical signs of disease. The animals showed no signs of acute problems such as breathing problems, restlessness or difficulties in walking during the experimentation.

Baseline spatial acquisition and reversal learning

During the last day of acquisition (baseline) and subsequent analyses, the escape latency and swim path distance were not significantly different. In the course of the reversal acquisition training however, mice learned to locate the escape platform regardless of the treatment regime. The analyses of escape latency, swim path distance and swim speed are consistent with the aforesaid.

Further analyses showed that mice treated with 40 mg/kg bw of khat had higher escape latency on day 1 (t_4=4.12 p=0.015) and 2 (t_4=2.28 p=0.065) of reversal training relative to the baseline performance (Fig. 1a). The rest of reversal training days notably day 3 and 4 did not yield any statistical significance. The escape latency in mice treated with 120 mg/kg bw of khat extract shortened consistently during reversal training relative to the performance of the last day of acquisition training. By training days 3 and 4 the escape latency was significantly (t_4=−2.49 p=0.05) vs (t_3=−2.5 p=0.05) shorter compared to the pre-reversal performance. The highest (360) dose of khat extract influenced mice escape latency. In this treatment group, mice had higher (49.13, 33.5, 40.2 and 35.75 s.) escape latency during reversal learning phase compared to baseline performance (23.5 s). During day 1 of reversal learning the escape latency was significantly
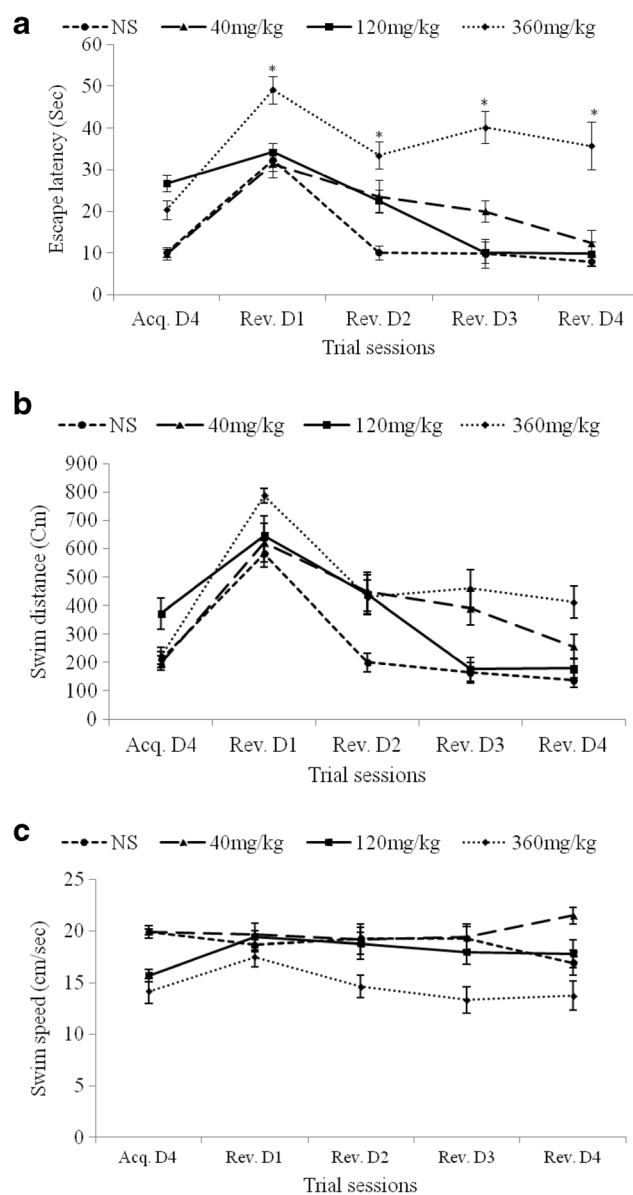

Fig. 1 **a** Escape latency during the last day of spatial acquisition and reversal learning in mice treated with NS, 40, 120 and 360 mg/kg bw of khat extract. Mice treated with 40 mg/kg bw of khat extract had significantly higher (P<0.05) escape latency by day 1 and 2 of reversal training compared to the baseline performance. The escape latency in mice treated with 120 mg/kg bw of khat extract shortened across days with reversal day 3 and 4 significantly (p<0.05) affected. Treatment of mice with 360 mg/kg bw khat significantly (p<0.05) increased the escape latency (*) across the reversal learning phase relative to baseline and control performance **b** Swim path distance during the last day of spatial acquisition and reversal learning in mice treated with NS, 40, 120 and 360 mg/kg bw of khat extract. The swim distance was significantly (p<0.05) longer in mice treated with 40 mg/kg bw of khat extract during reversal training day 1 and 2 relative to baseline. Swim distance was not affected by treatment of mice with 120 mg/kg bw of khat extract. The swim distance was significantly longer (p<0.002) on reversal training day 1 relative to acquisition training **c** Swim speed during the last day of spatial acquisition and reversal learning in mice treated with NS, 40, 120 and 360 mg/kg bw of khat extract. The analyses of baseline performance showed that mice treated with 120 and 360 mg/kg bw were significantly (p<0.05) slower than the controls. However, following reversal training, the significant difference in the swim speed appeared to be lost

higher (t_3=2.83 p=0.062) but the rest of the days performance except day 4 failed to yield statistical significance. The terminal evaluation of the reversal training performance showed that mice treated with 360 mg/kg bw had significantly higher (t_3=2.57 p=0.05) escape latency relative to the controls. However, the rest of the treatment regimes (40 and 120) did not yield significant difference on this parameter.

The analyses of swim distance showed that mice treated with 40 mg/kg bw of khat had significantly longer (t_4=3.89 p=0.018) and (t_4=2.51 p=0.06) on reversal training day 1 and 2 (Fig. 1b). The rest of the training days did not yield any statistical difference. Similarly, mice treated with 120 mg/kg bw khat extract failed to reach statistical significance on swim distance across the days of reversal training relative to the baseline acquisition training. On the other hand, treatment with 360 mg/kg bw of khat extract affected the swim distance. The swim distance was significantly higher (t_3=11.09 p=0.002) on reversal training day 1 relative to pre-reversal training performance. The rest of the training days did not yield any significant difference.

A paired t-test showed the swim speed to be slower in mice treated with 120 (t_4=6.21 p=0.003) and 360 (t_4=2.57 p=0.06) mg/kg bw of khat extract relative to controls on the last day of acquisition training (Fig. 1c). However, by the last day (day 4) of reversal learning, the statistical significance had been dissipated. Treatment with 120 mg/kg bw of khat extract yielded no significant difference (Fig. 1c).

Reference (long-term) memory

Post acquisition probe trial

During the post acquisition probe trial, the target was in S.E quadrant. A paired t-test revealed that mice treated with 40, 120 and 360 mg/kg bw of khat extract and controls, spent more time in target quadrant (Fig. 2). Further analyses with a paired t-test showed that mice treated with 40 mg/kg bw khat spent significant time (t_4=5.05 p=0.007) in the target and adjacent (t_4=2.65 p=0.057) quadrants than in the farthest quadrant. Further mice treated with 120 and 360 mg/kg bw khat extract spent significantly longer time (t_4=3.45 p=0.052) and (t_4=6.47 p=0.050) than in the other quadrants.

Post reversal probe trial

During the reversal probe trial, the target was in NW quadrant (Fig. 3). A paired t- test did not yield any statistical significance in terms of preference for target NW (22.5) compared to SE (12.9), SW (12.9) and NE (11.8) quadrants among mice treated with 40 mg/kg bw khat extract. Mice treated with 120 mg/kg khat extract showed significant preference for target (NW) compared to SE (t_3=−2.89 p=0.063) and SW (t_3=−4.94 p=0.016) quadrants, respectively. There was no
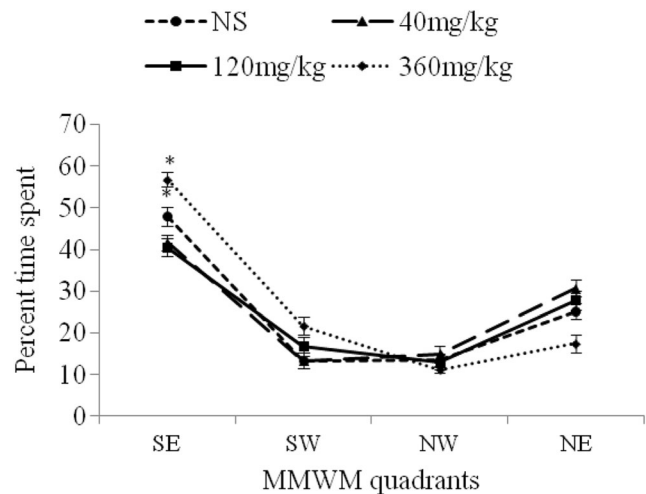

Fig. 2 Time spent in MMWM quadrants during post acquisition probe trial (long-term memory assessment) in mice treated with NS, 40, 120 and 360 mg/kg bw of khat extract. All mice groups and controls spent high % of time in the target (SE) quadrant. A paired t-test showed that mice treated with 40, 120 and 360 mg/kg bw khat extract spent significantly (p<0.05) higher percentage of time (*) in the target relative to adjacent and furthest quadrants

statistical difference (t_3=−1.19 p=0.32) between target and NE quadrants (25.3 vs 16.8 s). Mice treated with 360 mg/kg bw khat extract did not show any quadrant preference. Although, additional analyses showed that mice treated with the highest khat dose spent relatively more time in the old target (SE) (19.9) compared to the new (NW) (16.9), the difference was not statistically significant (t_3=0.29 p=0.79). Further analyses showed that mice treated with 120 mg/kg bw had marginal shorter time spent (t_3=−2.59 p=0.081) in
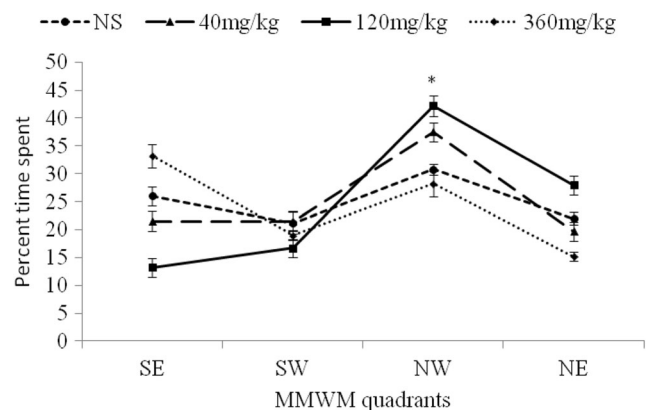

Fig. 3 Time spent in MMWM quadrants during post reversal probe trial (long-term memory assessment) in mice treated with NS, 40, 120 and 360 mg/kg bw of khat extract. Mice treated with different khat extract doses displayed differential preference for the new (NW) target quadrant during reversal memory probe trial. Mice treated with 40 mg/kg showed preference for target quadrant but there was no significant difference. Mice treated with 120 mg/kg khat extract spent more (P<0.05) time (*) in the target compared to other quadrants. Mice treated with 360 mg/kg body weight khat extract showed preference the old target (SE) (19.9) compared to the new (NW) (16.9) target quadrant although the difference was not statistically significant

SE quadrant compared to the controls. Additional analyses revealed that mice treated with 360 mg/kg bw had shorter time spent in NE quadrant ($t_3=-5.89$ $p=0.010$) compared to the controls.

Discussion

A comparative analyses of spatial acquisition, reversal learning and reference (long-term) memory in khat treated vs control mice is reported. The results showed that reference memory during post acquisition phase was retained across the treatment regimes. However, khat extract inhibited both learning and reference memory during reversal phase in a dose dependent manner. These differential effects of the extract on spatial learning and memory may be attributed to short as well as long term deleterious effects of khat on working memory and cognitive flexibility (Colzato et al. 2011; Hoffman and al'Absi 2013). The extract may have also modulated its effect possibly through structural modification of the brain similar with amphetamines (Yucel et al. 2007) and/or khat induced mental impairment (Odenwald et al. 2009; Balint et al. 2009).

On the acute usage, khat appeared to spare learning and memory performance. This is consistent with the fact that khat has been used for studying among students possibly because it improves memory through prevention of fatigue, improvement of concentration and flow of ideas (Gray and Roth 2007; Kalix 1992; Balint et al. 2009) or perceived believe of improving memory (Mohammed et al. 2014, 2015). Similarly, improved performance by mice after khat use has been reported with spatial learning and memory among rodents (Kimani and Nyongesa 2008). However, recent findings have shown that, khat extract administered on acute and sub acute basis impaired short term memory with no effect on long-term memory using spatial memory testing battery (Mohammed et al. 2014, 2015). These findings though similar to our results, depict some differences despite similar testing battery. These may have been attributed to differences in khat extraction, route of administration, animals, setting as well as testing protocols. The findings also parallel studies on amphetamines which have been implicated with increased rodent memory consolidation and reinforcement (Metzger et al. 1998; Killcross et al. 1994) including Morris water maze tasks (Brown et al. 2000).

Our high khat extract dose inhibited reversal performance an indication of poor reversal learning. This implies that khat extract affected cognitive flexibility of rodent (Colzato et al. 2011). This phenomenon has been labeled perserverative behavior. The behavior is characterized by problem (inflexibility) of switching from one mode of response for a given stimulus to another. The behavior has been attributed to disturbance of executive function and/or lesions in the striatum and basal ganglia (Devan et al. 1996; Kirkyby 1969).

Perserverative behaviour may also arise from inability to inhibit ongoing action or as a failure to initiate next response (Devan et al. 1996; Russing et al. 2003), a sort of behavioral rigidity. Khat has been implicated with impairment of cognitive flexibility in humans (Colzato et al. 2011). Whether, our neurobehavioral findings are as a result of effect of the present khat extract regime on mice structural, neurochemical and/or molecular (Yucel et al. 2007) changes in the relevant brain circuitry remains to be confirmed.

Neural-behavioral changes seen in amphetamine users have been attributed to altered dopaminergic transmission in the prefrontal cortex and/or striatum (Pezze et al. 2002) in the absence of reduced motivation and impaired cognitive performance (Lin et al. 2002). Such neuro-chemical changes may represent neuro-adaptive changes developed during repeated psychostimulants exposure. The brain structures known to undergo adaptive changes during repeated amphetamine administration, including the striatal complex, prefrontal cortices and limbic areas, have also been implicated in various forms of learning and memory (Robinson and Kolb 1997; Berke and Hayman 2000). Whether our study findings are as a result of this mechanism remains to be elucidated.

Repeated psycho-stimulants use and/or abuse including amphetamine and possibly amphetamine-like khat have been implicated with psycho-pathology resembling acute schizophrenic phenotype resulting from structural, molecular, neuro-chemical and neuro-physiological changes (Segal and Kuczenski 1997). Cognitive impairment is a key feature of patient with schizophrenia and an important determinant of the outcome and a target for therapy (Keefe and Harvey 2012). The impairment is attributable to diffuse abnormalities in frontal cortex, hippocampus and other cognitive modulating structures (Meltzer and Sumiyoshi 2008). Physiologically, the impairments are associated with deficits in glutamatergic, GABAergic, dopaminergic, cholinergic and serotonergic neurotransmitter systems. Serotonergic neurotransmitter system contribute to the deficit through its influence on dopaminergic, cholinergic, glutamatergic, GABAergic and growth factors and receptor functions all important in schizophrenia and cognitive status (Gray and Roth 2007; Millan 2000; Küçük et al. 2008; Mora et al. 1997; Zhou et al. 2008; Bantick et al. 2001). Additional studies are required to determine the specific neural mechanisms responsible for the observed patterns on learning and memory.

Our findings show an evidence for biological plausibility that chronic khat use may induce memory deficits and impair cognitive flexibility. The differential patterns of memory deficits may reflect the differences impact of dose effect as well as time dependent impairment. Further studies are needed to unravel the mechanism involved in these neuro-cognitive effects of khat. Such studies will inform the choice for interventions to reduce the burden of khat associated neuro-cognitive impairments.

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