
## Jornades de Foment de la Investigació

# DOPAMINE/ ADENOSINE INTERACTION IN EFFORT-RELATED PROCESSES IN RODENTS: STUDIES USING T-MAZE PARADIGM IN MICE

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**Agradecimientos:**
Proyecto financiado por Conselleria de Sanitat. Generalitat Valenciana. (AP-041/08).

## ABSTRACT:

Humans and animals realize cost/benefits analysis of our responses with the goal of use the lowest energy possible to obtain the major benefit. Mesolimbic dopamine (DA) is a critic component in the cerebral circuitry regulating decision making based on the effort that the response requires, because it regulates behavioral activation. Research with rodents show that DA antagonists displace the behavior from the response that supposes more effort, though it has more reinforcement, to other behavior with less effort required. Interaction between A2A adenosine receptors and D2 receptors play an essential paper in these processes. In the T-Maze paradigm the animal is exposed to an option of choose one arm with two food pellets, to which it accedes after climbing a 14 cm barrier, or to choose the arm without barrier and with only one food pellet. Control animals choose to do the effort of climbing the barrier to obtain the high reinforcement. Haloperidol, D2 antagonist, produces change behavior towards the less density arm, been this effect partially reverted with theophylline, unspecific adenosine antagonist, and with MSX-3, selective A2A antagonist. These drugs could have applications for the treatment of amotivational syndromes.

## INTRODUCTION

*Definition and components of motivation*

Motivation has been defined as the set of processes through which organisms regulate the probability, proximity and availability of certain stimuli (Salamone, 1992; Salamone and Correa, 2002). Through motivational processes organisms direct their efforts towards a certain goal, whether it is consuming food, drinking or engaging in mating behavior (Salamone et al., 1992). Thus, motivation plays an integral role in the execution of decision making in everyday life. As different reinforcing stimuli involve varying work requirements, organisms make effort related choices based upon analyses of the energy cost of the action relative to the magnitude of the organism's benefit from such actions. The employment of cost/benefit analyses determine the executed behavior of the organism and are crucial to motivational processes (Salamone and Correa, 2002). Additionally, obstacles such as environmental constrains play an integral role in such cost/benefit analyses. Instrumental behaviors often entail a high degree of vigorous work output from the organism to overcome such barriers to obtain the reinforcer (Salamone and Correa 2002; Farrar et al., 2007). In behavioral research, two prominent aspects of motivational processes include directional or goal directed behaviors, aspect of motivation that refers to the fact that motivated behavior is either directed towards or away from a particular stimulus, and the activational aspects of motivated behaviors, pertaining to the speed, vigor and persistence in the pursuit of a reinforcing stimulus (Salamone and Correa, 2002).

The concepts of "drive" and "incentive" offered by Hull et al. (1991) and Spence (1956) emphasized that motivational conditions can produce energizing effects on behavior. Researchers who conducted early studies of the neural basis of motivation and emotion emphasized the role that arousal and "energy mobilization" played in these processes (e.g., Lindsley 1951; Moruzzi and Magoun 1949; Rubio-Chevannier et al. 1961).

It has been suggested that interference with DA transmission impairs activational aspects of food motivation but leaves intact directional aspects (Salamone 1988, 1997, 1992; Barbano and Cador 2006). This idea is not only related to locomotion or schedule-induced activity but is also highly relevant for food-reinforced instrumental behaviors. Lots of studies demonstrate that the effects of dopaminergic manipulations on indices of behavioral activation in food related tasks are not simply dependent upon changes in primary food motivation or appetite. Instead, the preponderance of evidence suggests that these experiments serve to dissociate dopaminergic involvement in behavioral activation from processes mediating primary food motivation or appetite (Salamone 1988, 1992; Salamone et al. 1997, 2003; Kelley et al. 2005). Consistent with this, it has been suggested that interference with DA transmission impairs activational aspects of food motivation but leaves intact directional aspects (Salamone 1988, 1997, 1992; Barbano and Cador 2006).

*Neuroanatomy of Motivation: The Basal Ganglia*

Basal ganglia (BG) consist of a collection of forebrain nuclei relevant for the control of a variety of behavioral functions, among which can be included motor and non motor functions (McDonald & White, 1993; Redgrave et al., 1999).

Traditionally the nuclei included in the BG are striatal areas such as the caudate, putamen, nucleus accumbens (Nac), and globus pallidus. Associated areas include the substantia nigra and the subthalamic nucleus. Collectively, the caudate and putamen are referred to as the dorsal striatum whereas the Nac and olfactory tubercle are often collectively referred to as the ventral striatum (Nolte, 2007). BG as a whole serves as one of many circuits involved in motor function and motivated behaviors.
The Nac is a subregion of the ventral striatum, a collection of neurons located at the junction of the head of the caudate and the septum pellucidum (Kelley et al., 1997; Salamone, 1996). The Nac can be divided into core and shell subregions based on anatomical and biochemical differences (Jongen-Relo et al., 1993, 1994; Meredith et al., 1993; Voorn et al., 1994; Zaborszky et al., 1985), of which it has been shown that different effects on motor function occur based on the location of the Nac subdivisions (Heimer et al., 1987; Ishiwari et. al., 2007). Mogenson and colleagues (1980) suggested that Nac serves as a "limbic-motor" interface that translates motivational and cognitive information into action. Distinct subregions and cell groups in nucleus accumbens act as "gates" that allow

multiple channels of information to be processed, and the neurotransmitter DA, along with GABA, glutamate, acetylcholine, adenosine and other substances, regulate the physiological responses of accumbens neurons.

*Dopamine in the Striatum*

In terms of DA transmission throughout the brain, there are four DA pathways (Nolte, 2007). The mesolimbic pathway stems from the VTA and provides the source of the dopaminergic innervation to the Nac. It is this pathway that is thought to be involved in motivated behaviors.

DA in the Nac appears to be one of the critical components of the brain circuitry controlling effort-related behavioral processes and behavioral activation (Salamone et al., 1991, 1997, 2002, 2003, 2005, 2007; Yurgelun-Todd et al., 2007; Barbano and Cador 2007; Niv et al., 2007; Phillips et al., 2007; Robbins and Everitt 2007).

*Adenosine in the Striatum*

Recently it has been shown that adenosine plays a role in the modulation of DA transmission within the brain and drugs that act on adenosine have been investigated for their potential to serve as a novel treatment for Parkinson's disease (Correa et al. 2004; Ishiwari et al. 2007; Betz et al., 2009). Central adenosine neurotransmission plays an important role in modulating the functional circuitry of the basal ganglia (Ferré et al., 1997; Svenningsson et al., 1999; Hauber et al., 2001). DA and adenosine receptors are known to share a considerable overlap in their regional distribution, being the BG a rich place in colocalization of both type of receptors (Short et al., 2006).

A1 and A2A receptors are robustly expressed in the BG, with the A2A subtype predominantly expressed in the striopallidal neurons of the "indirect" pathway and Nac (Jarvis and Williams 1989; Schiffmann et al., 1991; DeMet and Chicz-DeMet, 2002; (Ferré et al., 1997; 2004).

This high density of A2A receptors within the ventral striatum, particularly in the Nac, also may be an important component of current motivational research, as it has been suggested that adenosine also plays a role in aspects of motivated behaviors (Salamone et al., 2007; Farrar et al., 2007). While central A2A receptors are expressed almost exclusively in the striatum (Ferre et al., 1993; Pinna et al., 2005; Svenningsson et al., 1997; Tanganelli et al., 2004), A1 receptors have a relatively high expression throughout the brain; highest densities are found in the stratum oriens, hippocampus, cerebral cortex, striatum and thalamus (Fastbom et al., 1986, 1987a,b; Svenningsson et al., 1997).

*Cellular interactions of A2A and $D_2$ receptor subtypes*

The cellular and molecular bases of the interactions of adenosine and dopamine receptors colocalized in striatum have been the subject of considerable interest within the last few years, and several possible molecular mechanisms for this interaction have been proposed, among these include the finding that D2 receptors and A2A receptors (Fink et al., 1992; Ferré 1997; Svenningsson et al.,1999; Hillion et al., 2002; Fuxe et al., 2003), as well as D1 receptors and A1 receptors (Gines et al., 2000), have been shown to form heteromeric receptor complexes.

In the neostriatum, D2 receptors and A2A receptors appear to have opposite functional interactions (Ferré et al., 1997). Researchers have recently begun to identify additional functions of adenosine $A_{2A}$ receptors related to cognition (Takahashi et al., 2008) and motivation (O'Neill and Brown 2006; Farrar et al., 2007; Font et al., 2008; Mingote et al., 2008; Worden et al., 2009; Salamone et al., 2009; Mott et al., 2009).

*Dopaminergic involvement in aspects of motivation*

The dopamine (DA) hypothesis of 'reward' or reinforcement has become one of the most ubiquitous and popular hypotheses in the history of neuroscience. According to this hypothesis, DA systems mediate the reinforcing effects of several different classes of stimuli (see Salamone and Correa, 2002). Considerable research with the taste reactivity paradigm has demonstrated that interference with DA by systemic administration of DA antagonists or by local depletions of DA in nucleus accumbens or neostriatum failed to alter appetitive taste reactivity for sucrose (Berridge et al., 1998; Treit and Berridge, 1990). Pleasure or primary appetitive motivation, are aspects of the motivated behavior that are preserved after DA transmission interference (Salamone et al., 2007).

Substantial evidence indicates that DA systems are involved in activational aspects of motivation (Salamone 1992; Salamone et al 1994; Cousins et al., 1996; Salamone et al., 1997; Cousins et al., 1999; Correa et al., 2002; Farrar et al., 2007). It has been shown that DA receptor antagonism or Nac DA depletions induce behavioral impairments that make animals sensitive to work-related response costs (Salamone 2007), thus regulating effort-related processes (Salamone, 1988, 1991, 1992; Salamone et al., 1991, 1997, 2003, 2005; Vezina et al., 2002; Zhang et al., 2003; Wakabayashi et al., 2004; Barbano and Cador, 2006; Denk et al., 2005). DA, particularly in the Nac, mediates effort related choices (Salamone et al., 1992, 2003, 2005; Denk et al., 2005). Thus, modulating modulates the outcome of cost/benefit analyses (Salamone et al., 1991, 1992, 1993, 1994, 2003, 2005; Cousins et al, 1994, 1996; Nowend et al. 2001; Farrar et al., 2007).

*Dopamine-Adenosine interactions on motor and motivated behaviors*

In addition to studying DA systems, there has been a growing interest in the last few years that has focused upon the interaction between DA and the neuromodulator adenosine.

There is evidence suggesting that DA-adenosine interactions are involved in accumbens-mediated behaviors. MSX-3 (A2A selective receptor antagonist) augmented bar pressing in a FR5 program in rats pretreated with haloperidol (D2 receptor antagonist) (Farrar et al., 2007; Mott et al., 2009). The same doses administered alone did not produce any effect. Furthermore, this effect is mediated by the interaction adenosine/D2 and not with D1 (Worden et al., 2009).

Studies on the motivational significance of the interaction between DA and adenosine transmission in the brain have garnered increasing attention in the scientific community (Farrar et al., 2007; Worden et al., 2009; Salamone et al., 2009; Mott et al., 2009).

The T-Maze choice procedure was also developed to study in rats effort based decission making in motivated behavior (Salamone et al., 1994; Cousins et al., 1996). In this procedure, two arms of the maze have different assigned food densities (four pellets vs. two or four vs. zero). Rats are allowed the choice to go and consume a lower amount of food (e.g. 2 pellets) in the low density (LD) arm, or obtaining a larger amount of food in the high density (HD) arm, which typically is blocked by placement of 44 cm vertical barrier. Rats must then choose either to consume a reduced amount of food in the LD arm or scale the barrier to consume a higher amount of food in the HD arm. Depletion of accumbens DA or treatment with haloperidol dramatically altered choice behavior when the HD arm containing four pellets was blocked by a barrier and the LD arm contained two pellets. Rats showed a significant decreased selection of the HD arm and a significantly increased selection of the LD arm (Cousins et al., 1996; Salamone et al., 1994). Under test conditions in which no barrier was present, rats treated with haloperidol or nucleus accumbens DA depletions did not show a behavioral allocation from the HD arm to the LD arm in (Salamone et al., 1994). When the HD arm contained four pellets blocked by a barrier, but the low density arm contained no pellets, rats with accumbens DA depletions chose to climb the barrier and consume the pellets (Cousins et al., 1996). Rats treated with 0.1 mg/kg haloperidol and Nac DA depletions showed significantly increased response latencies in both the barrier and non barrier conditions (Salamone et al., 1994; Cousins et al., 1996). These results indicate that blockade or depletion of DA did not affect the primary reinforcing nature of food, but rather that Nac DA depletions affected the relative allocation of effort-related choice behaviors regarding high energy work requirements.

In a recent paper (Mott et al., 2009), it was found a significant dose-related reversal effect of MSX-3 on haloperidol induced shift in the T-maze paradigm with rats (0.75, 1.5 and 3 mg/kg MSX-3). However, with DPCPX (A1 receptor antagonist) no reversal effect was seen.
The present experiments were designed to investigate the ability of an adenosine receptor antagonist to reverse the behavioral impairment in T-maze choice induced by blockade of dopaminergic transmission with the D2 receptor antagonist haloperidol.

## MATERIALS AND METHODS:

### Subjects

CD1 male mice (20±2 g), 4 weeks old upon arrival to the laboratory were purchased from Harlan-Interfauna Ibérica S.A. (Barcelona, Spain). A total of 38 animals were used in the present studies. Mice were housed in groups of three per cage with standard laboratory rodent chow and tap water available ad libitum. They were maintained in the colony for 7 days prior to experimentation at 22 ± 2 ºC with lights on from 0800 to 2000 hours. Mice started to be tested after 11 weeks after arrival to the laboratory. Mice weighted 27-33 g at the beginning of the study, after that, mice were food-deprived to 85% free-feeding body weight throughout the study with water available ad libitum in the home cages. All experimental procedures complied with European Community Council directive (86/609/ECC).

### Pharmacological agents and selection of doses

Haloperidol (Sigma Química C.O), a D2 dopamine receptor selective antagonist, was dissolved in a 0.3% tartaric acid solution (pH=4.0). The doses used (0.0 / 0.025 / 0.05 / 0.1 mg/kg) were adapted from rat doses used in previous studies (Mott et al., 2009). Tartaric acid solution was the vehicle control for the haloperidol dose 0.0 mg/kg. Haloperidol was administered 50 minutes before the test.

Theophylline (TOCRIS Bioscience), a nonspecific adenosine receptor antagonist, was dissolved in 0.9% w/v saline (pH= 7.4). The doses used (0.0 / 5 / 10 / 15 mg/kg) were adapted from mice and rat doses used in previous studies (Malec and Poleszak, 2006; Bishnoi et al., 2007). Saline solution was used as a vehicle control for theophylline dose 0 mg/kg. Theophylline was administered 20 minutes before the test.

MSX-3 ((E)-phosphoric acid mono – [3-[8-[2-(3- methoxphenyl)vinyl] – 7- methyl-2, 6, - dioxo-1-prop-2-ynyl-1, 2,6,7 – tetrahydropurin- 3-yl] propyl] ester disodium sald) an A2A adenosine receptor selective antagonist synthesized at the laboratory of Dr.Christa Müller at the Pharmazeutisches Institut, Universität Bonn, in Bonn, Germany. MSX-3 was dissolved in 0.9% w/v saline (pH= 7.4). The doses used (0.0 / 1 / 2 / 3 mg/kg) were adapted from rat doses used in previous studies (Mott et al., 2009). Saline solution was used as a vehicle control for MSX-3 dose 0 mg/kg. MSX-3 was administered 30 minutes before the test.

All drugs were administered intraperitoneally (IP).

**Apparatus and testing procedures**

Each trial started when the gate in the central arm was opened. It finished when the animal started to consume the food located in the selected arm. Immediately after the animal finished consuming the food, it returned by itself to the starting arm where was briefly enclosed with the purpose of revealing the food. In each trial the mouse had the option of going to any of the two opposed arms to consume the pellets. When the mouse had chosen one arm the other arm was blocked. During the initial training trials the researcher had to return the animal to the starting arm. This procedure was repeated during 30 trials, and that was considered a session. Sessions started two hours after the colony lights where on. Animals had one training session per day, 5 days a week.

Mice were trained in several different phases. During the first training phase no barrier was present. The first 2 days of the initial training, mice had free access to both arms of the T-maze upon exiting the start arm and allowed to consume all pellets in both HD and LD arms of the maze before being returned to the start arm. Upon completion of this initial training, mice were then trained to select between the HD or the LD arm, with no barrier in place. The criterion before a new learning phase started was set so that animals had to choose 90% of the times the HD arm at least for 2 days. In the second phase a small barrier (5.5 cm high) was introduced in the HD arm. In the third phase a medium barrier (12 cm high) replaced the short one. Finally, in the fourth training phase and for the rest of the experiment, the high barrier (14 cm high) was introduced. During the test phase there was one drug day and 4 baseline days before the next drug day.

To validate the paradigm, other experiment was done where trained animals with the same procedure were trained in fifth phase with two 14 cm barriers, one in the HD arm and other in the LD arm. Test days the execution was evaluated of the described form previously. Animals receive 0 or 0.1 mg/kg haloperidol. Again, it was a within-groups design in a random order.

**RESULTS:**

During the following experiments, every day each animal had one training session starting two hours after the lights where on. Every training session consisted of 30 trials (See Fig. 1 for a model of learning progression, of one of the experiments done). The duration of the phases was:
Phase 1. No barrier: 3 weeks.

Phase 2. Barrier 5.5 cm high in HD arm: 1 weeks.
Phase 3. Barrier 12 cm high in HD arm: 1 weeks.
Phase 4. Barrier 14 cm high in HD arm: 2 weeks before drug test starts.

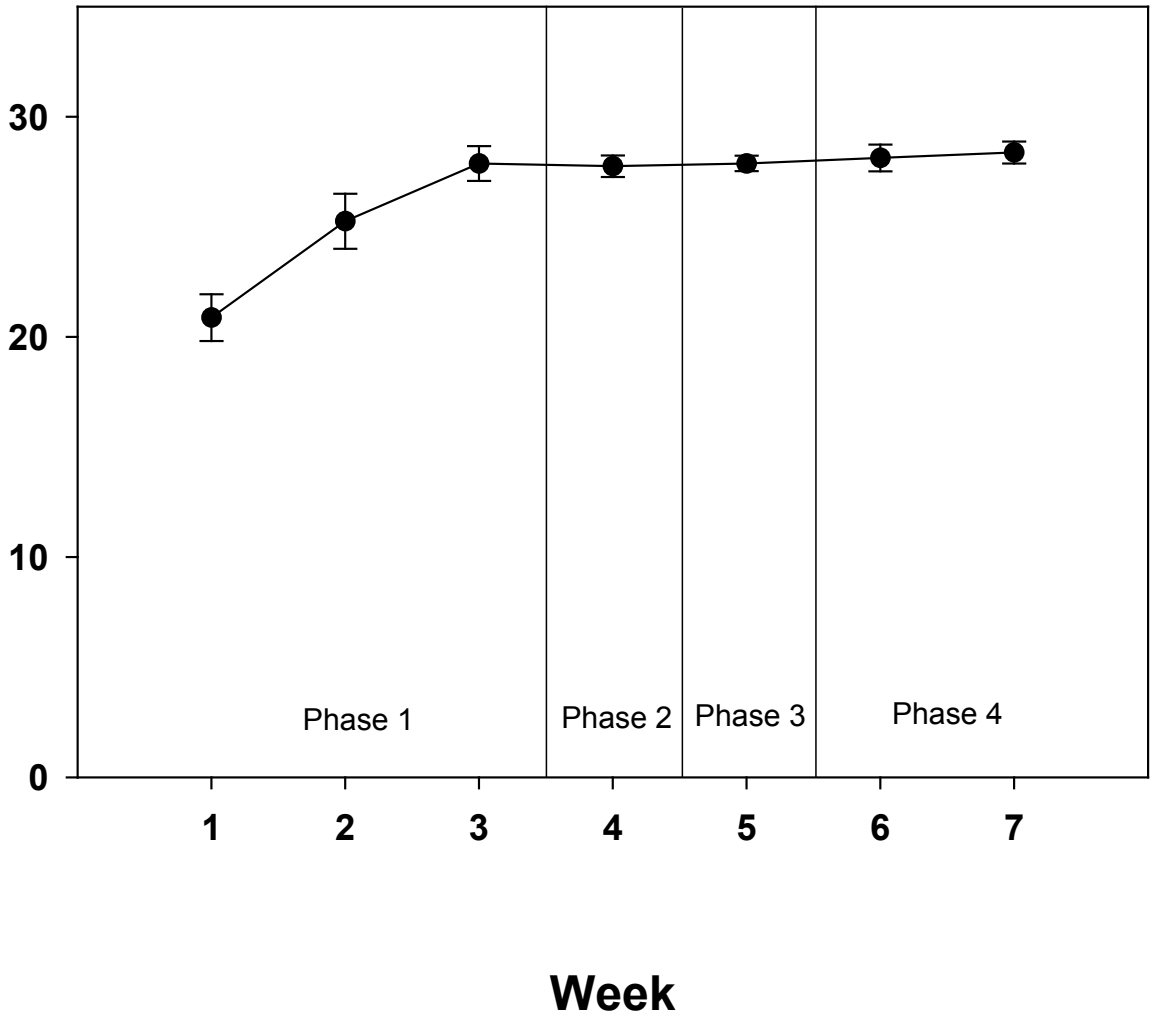


Fig.1 Mean + SEM number of HD arm selection by week during all the training phases.

**Experiment 1:** Effect of different doses of haloperidol on effort-related choice behavior

The data for selection of the HD arm (number of barrier crossings) are shown in Fig.1.1 Repeated measures ANOVA indicated a significant effect of haloperidol [$F(3, 18) = 3{,}175$, $p < 0{,}05$]. Planned comparisons showed that haloperidol decreased the number of HD arm selections in a significant manner, 0.05 ($p<0.05$) and 0.1 mg/kg ($p<0.01$).

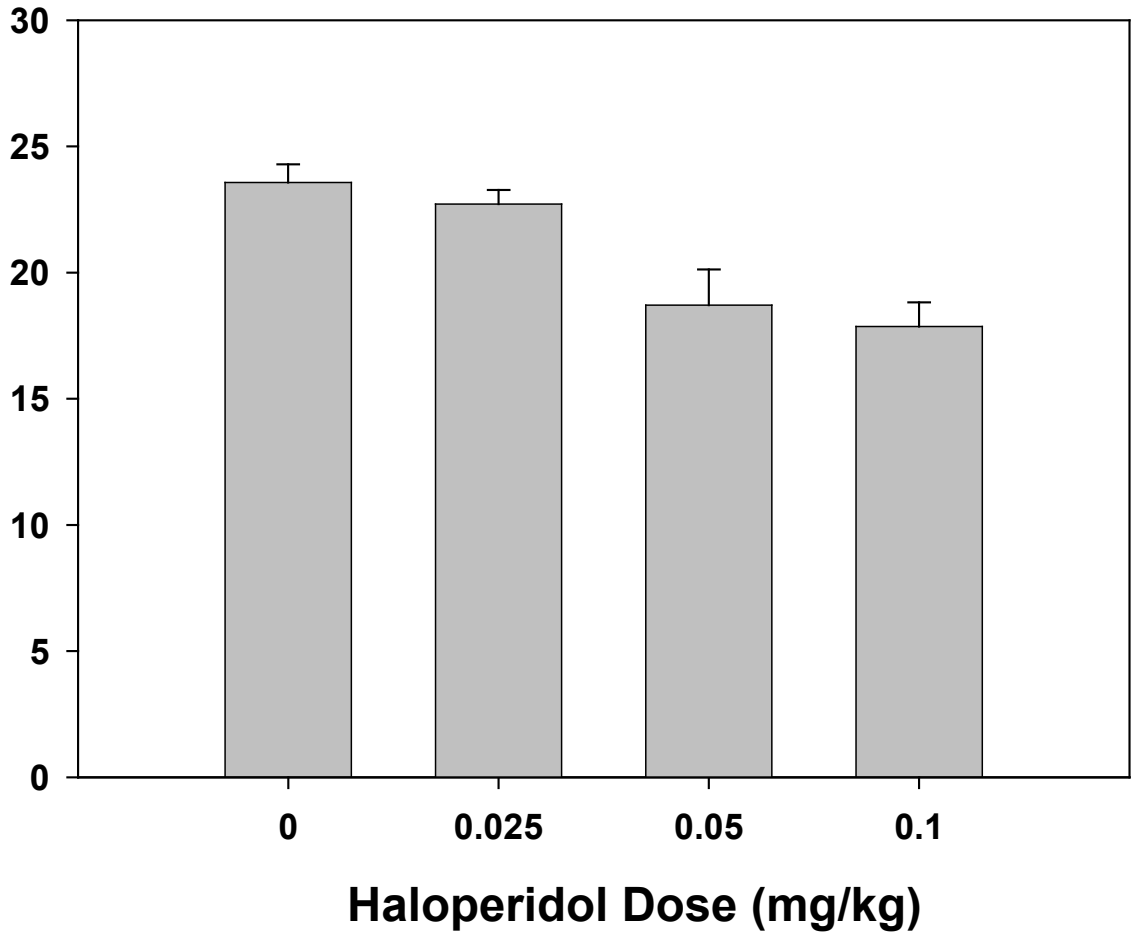


Fig. 1.1 Effect of IP administration of haloperidol on HD arm choice in the T-maze. Mean (±SEM) number of HD arm choices after treatment with haloperidol (0.0, 0.025, 0.05 and 0.1 mg/kg) administered 50 minutes before testing. *p<0.05 **p<0.01 significantly different from vehicle.

The data for latency to reach the food are shown in Fig.1.2. Repeated measures ANOVA showed a significant effect of haloperidol [$F(3, 18) = 3{,}175$, $p < 0{,}05$]. Planned comparisons revealed significant differences between the lowest dose of haloperidol 0.025 mg/kg and the highest dose 0.1 mg/kg ($p<0.05$).

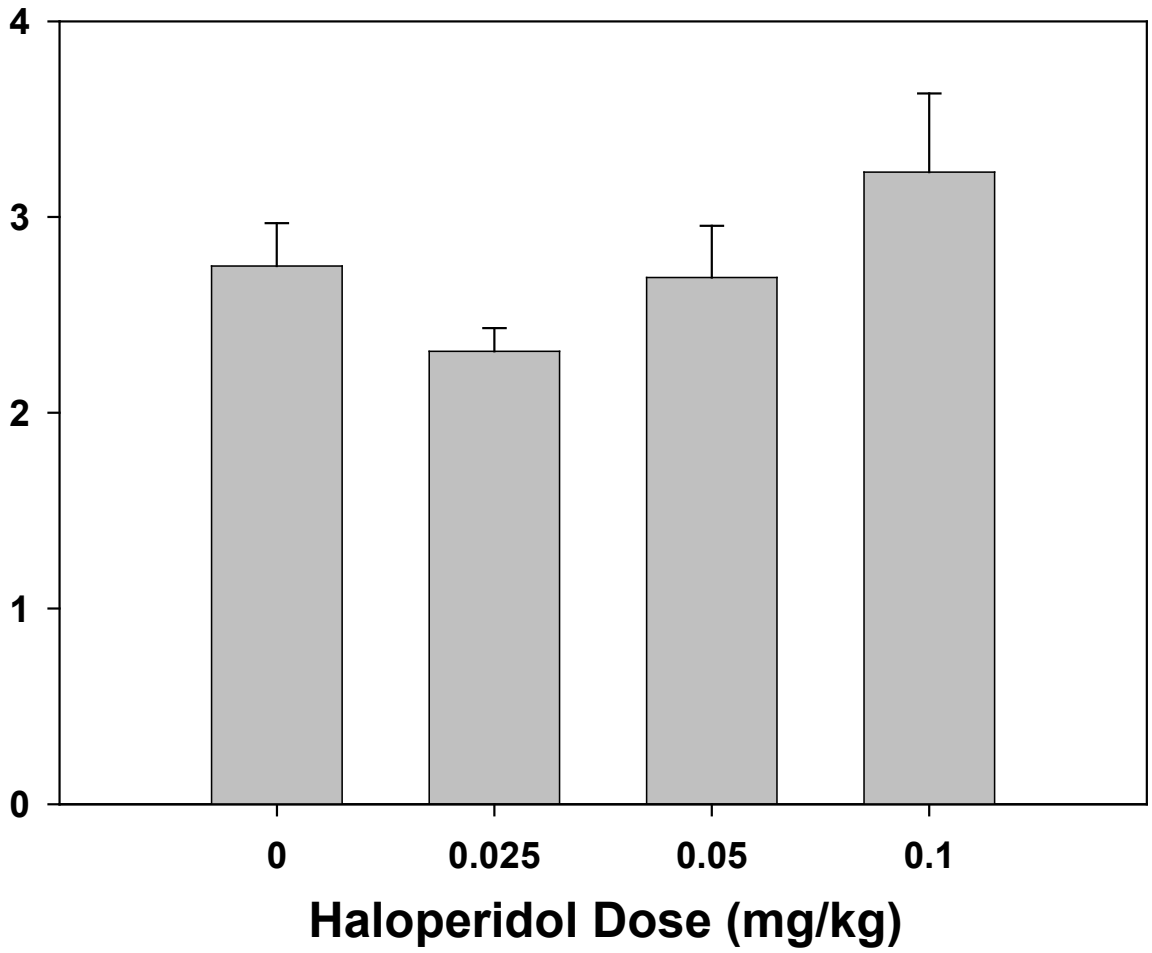


Fig. 1.2. Effect of IP administration of haloperidol on T-maze run latency in mice. Mean (±SEM) run latency (average in seconds across 30 trials) after treatment with haloperidol (0.0, 0.025, 0.05 and 0.1 mg/kg) administered 50 minutes before testing.

**Experiment 2:** Effect of haloperidol on choice behavior in a two barrier T-maze.

The data for selection of the HD arm are shown in Fig.2.1. Repeated measures ANOVA yield a non significant effect of haloperidol (0.0, 0.1 mg/kg).

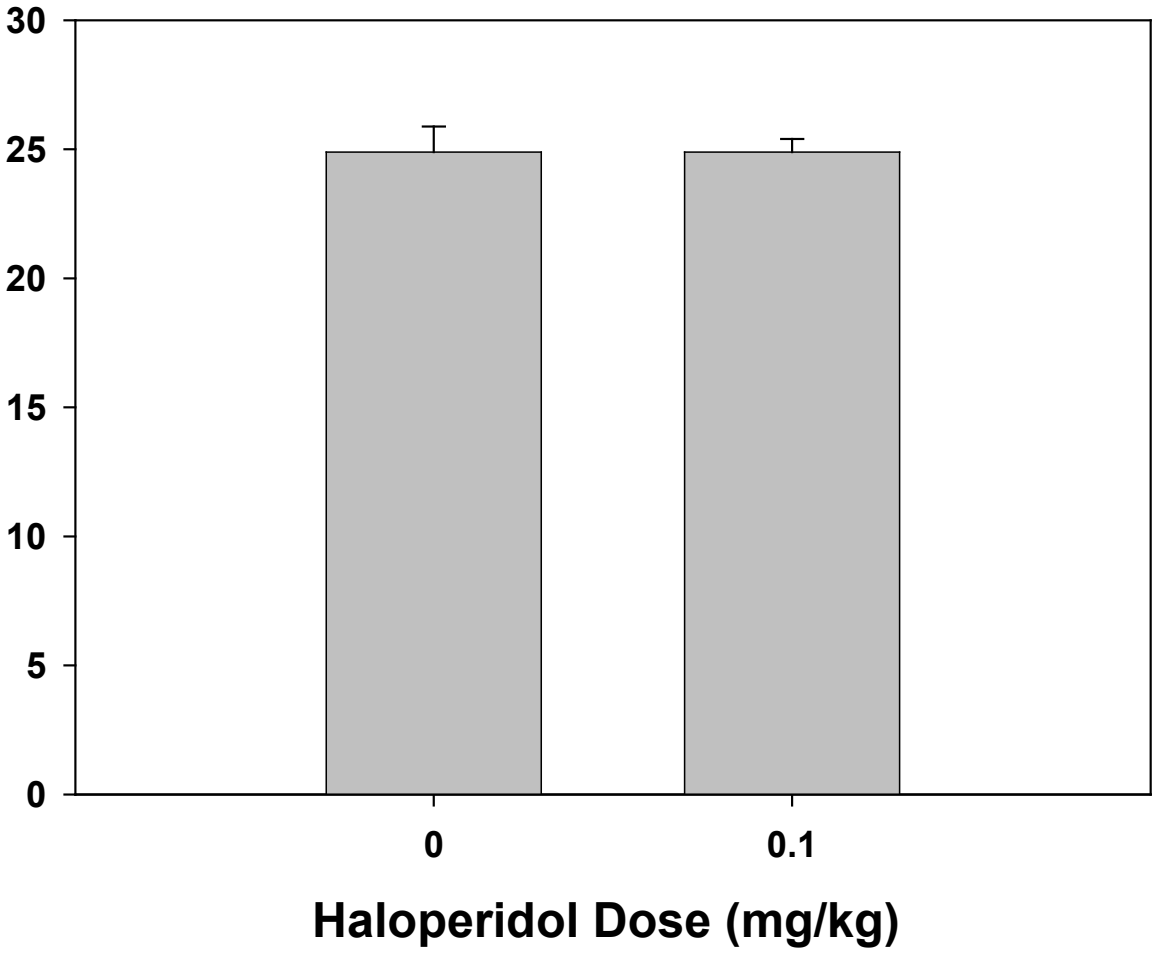


Fig. 2.1 Effect of IP administration of haloperidol on HD arm selection when the T-maze had two arms with barrier. Mean (±SEM) number of HD arm choices after the treatment with haloperidol (0.0 and 0.1 mg/kg) administered 50 minutes before testing.

The data for latency to reach the food are shown in Fig.2.2. Repeated measures ANOVA indicated a non significant effect of haloperidol doses (0, 0.1 mg/kg).

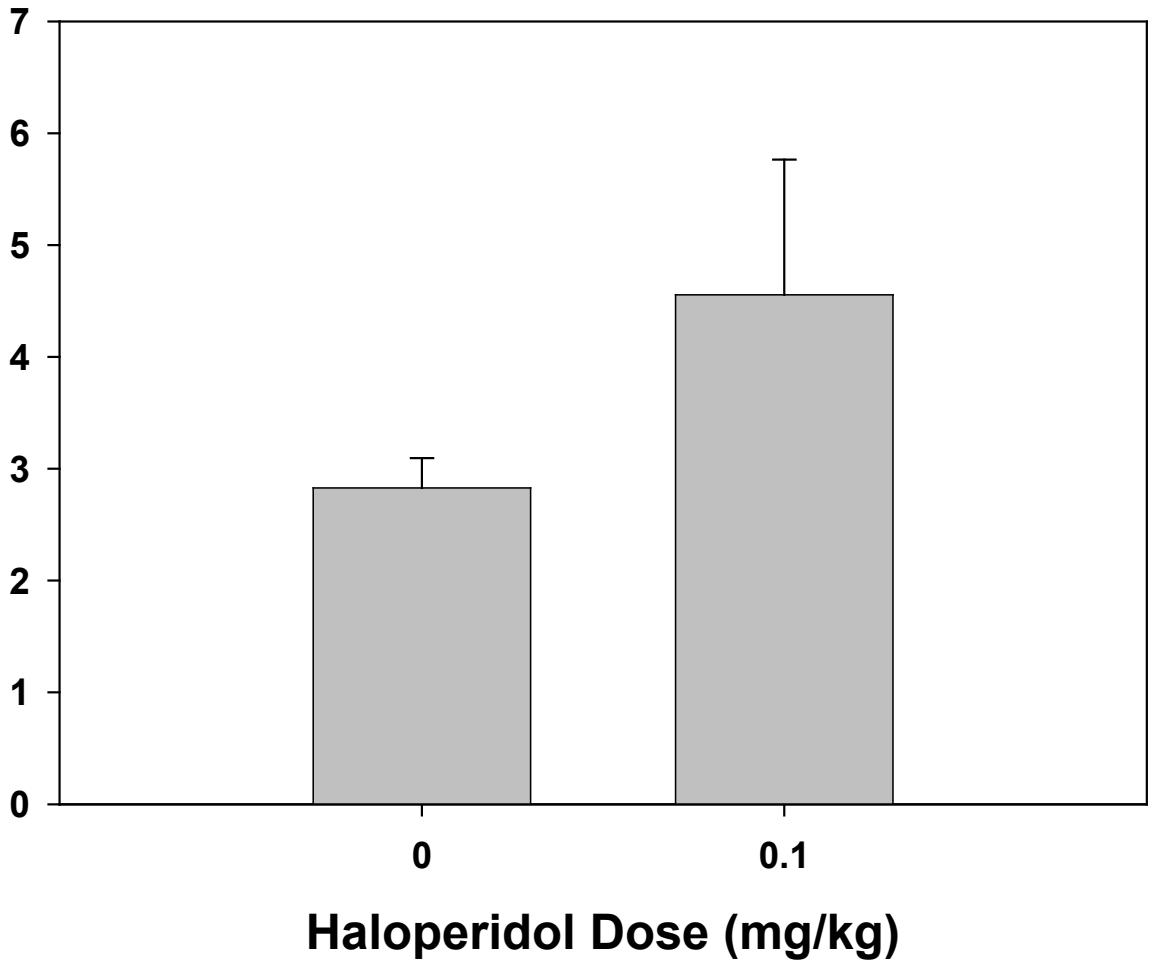


Fig. 2.2. Effect of IP administration of haloperidol on run latency in a T-maze with two barriers, in mice. Mean (±SEM) run latency (average in seconds 30 trials) after treatment with haloperidol (0.0 and 0.1 mg/kg) administered 50 minutes before testing.

**Experiment 3:** Theophylline modulation of haloperidol effects on effort-related choice in the T-maze.

The data for selection of the HD arm after co-administration haloperidol and theophylline are shown in Fig.3.1. Repeated measures ANOVA showed a significant effect of drug treatment [$F(4, 44) = 19.054$ , $p < 0.01$ ]. Planned comparisons revealed significant differences between control condition (veh/veh) and all other treatment conditions ($p<0.01$). The HP/Veh treated group was different from HP/10T and HP/15T ($p<0.05$).-

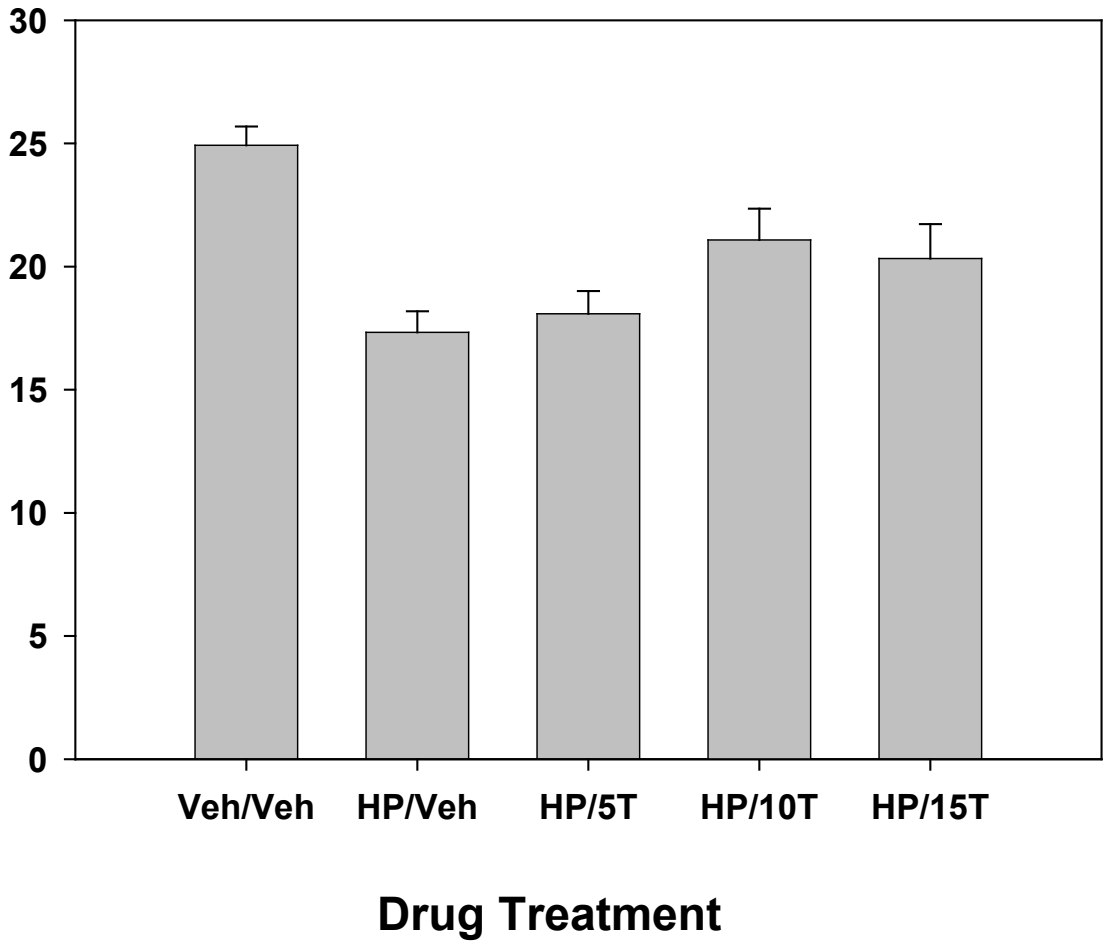


Fig 3.1. Effects of the nonspecific adenosine antagonist, theophylline, on T-maze arm choice in mice co-administered haloperidol. Mean (±SEM) number of HD arm choices after IP treatment with vehicle (Veh) or haloperidol (HP, 0.1mg/kg, 50 minutes before test) plus various doses of theophylline (T; 5.0, 10.0 and 15.0 mg/kg, 20 minutes before test) are shown. **p<0.01 significantly different from Veh/Veh; #p<0.05 significantly different from HP/Veh.

The data for general latency after co-administration haloperidol and theophylline are shown in Fig.3.2. Repeated measures ANOVA yield a non significant effect of theophylline treatment.

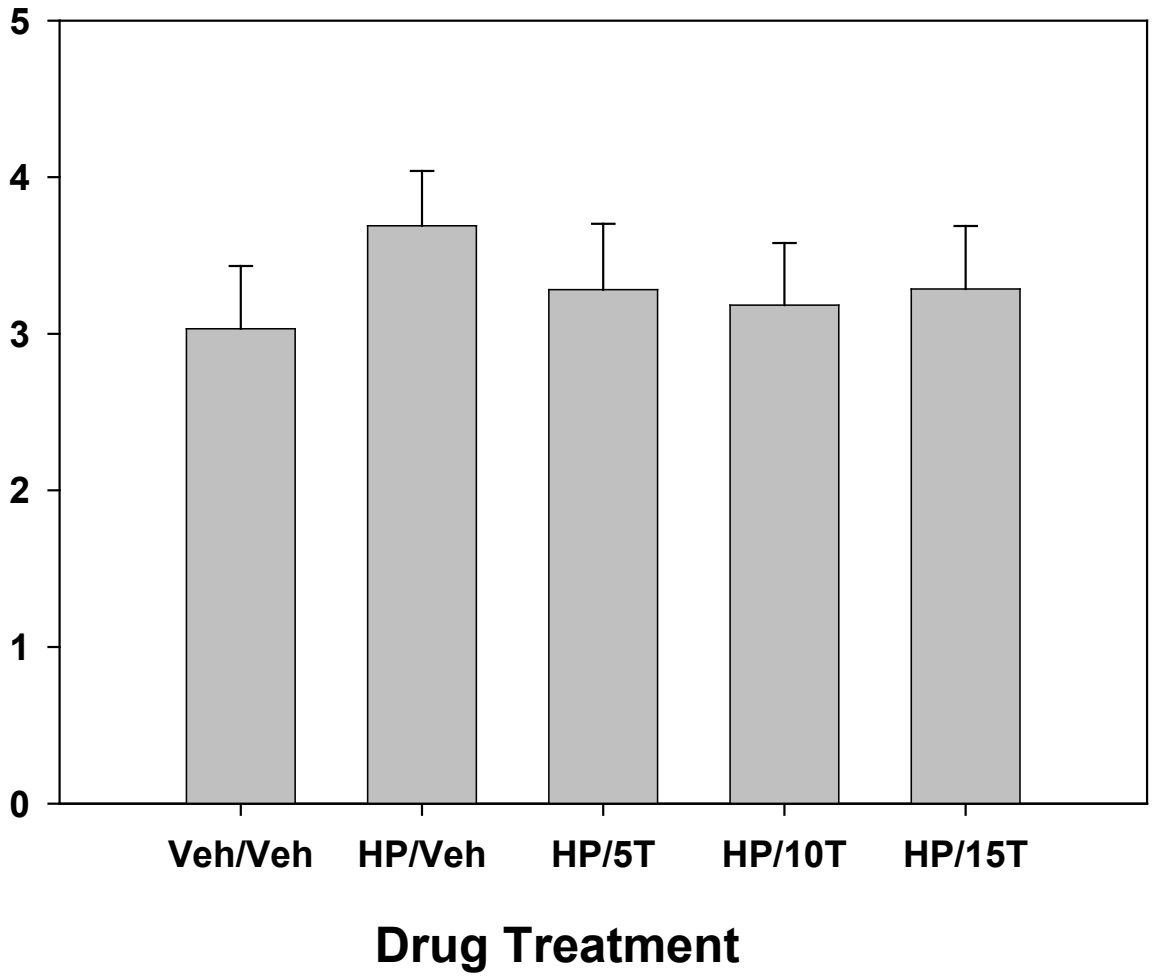


Fig. 3.2. Effects of the nonspecific adenosine antagonist, theophylline, on T-maze run latency in mice. Mean (±SEM) run latency (average in seconds across 30 trials) after IP treatment with vehicle (Veh) or haloperidol (HP, 0.1mg/kg, 50 minutes before test) plus various doses of theophylline (T; 5.0, 10.0 and 15.0 mg/kg, 20 minutes before test) are shown.

**Experiment 4:** MSX-3 modulation of haloperidol effects on effort-related choice in the T-maze.

The data for selection of the HD arm after co-administration haloperidol and MSX-3 are shown in Fig.4.1. Repeated measures ANOVA indicated a significant effect of drug treatment [ $F(4, 32) = 19{,}796$ , $p < 0{,}01$]. Planned comparisons revealed that HP/Veh was significantly different from the rest of conditions ($p<0.01$). There were no differences between Veh/Veh and HP/2M and HP/3M. There were not differences between Veh/Veh and the highest two doses of MSX-3.

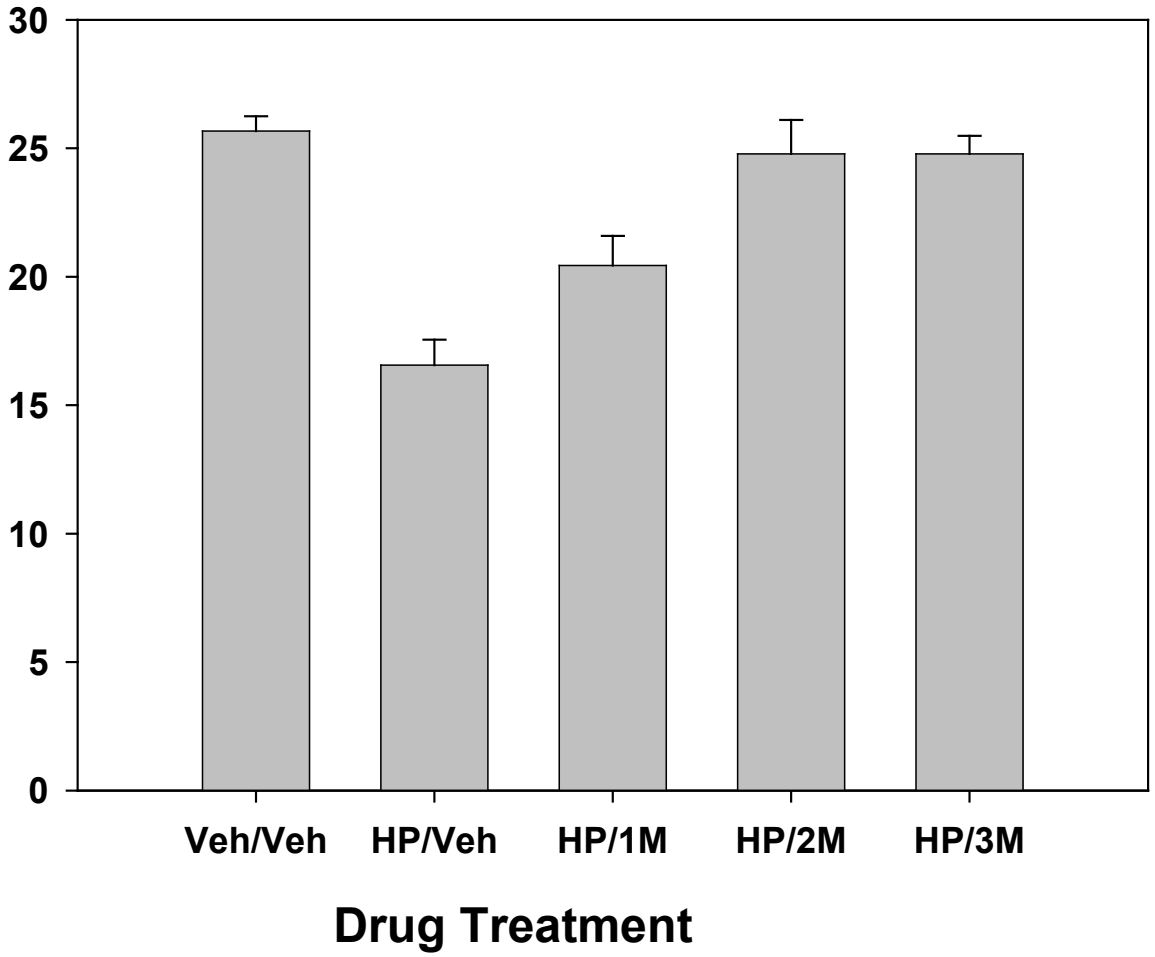


Fig. 4.1. Effects of the adenosine A2A specific antagonist, MSX-3, on T-maze arm choice in mice co-administered haloperidol. Mean (±SEM) number of HD arm choices after IP treatment with vehicle (Veh) or haloperidol (HP, 0.1mg/kg, 50 minutes before test) plus various doses of MSX-3 (M; 1.0, 2.0 and 3.0 mg/kg, 20 minutes before test) are shown. **p<0.01 significantly different from Veh/Veh; #p<0.05 and ##p<0.01 significantly different from HP/Veh.

The data for latency to reach the food after co-administration haloperidol and MSX-3 are shown in Fig.4.2. Repeated measures ANOVA indicated a non significant effect of MSX-3 treatment.

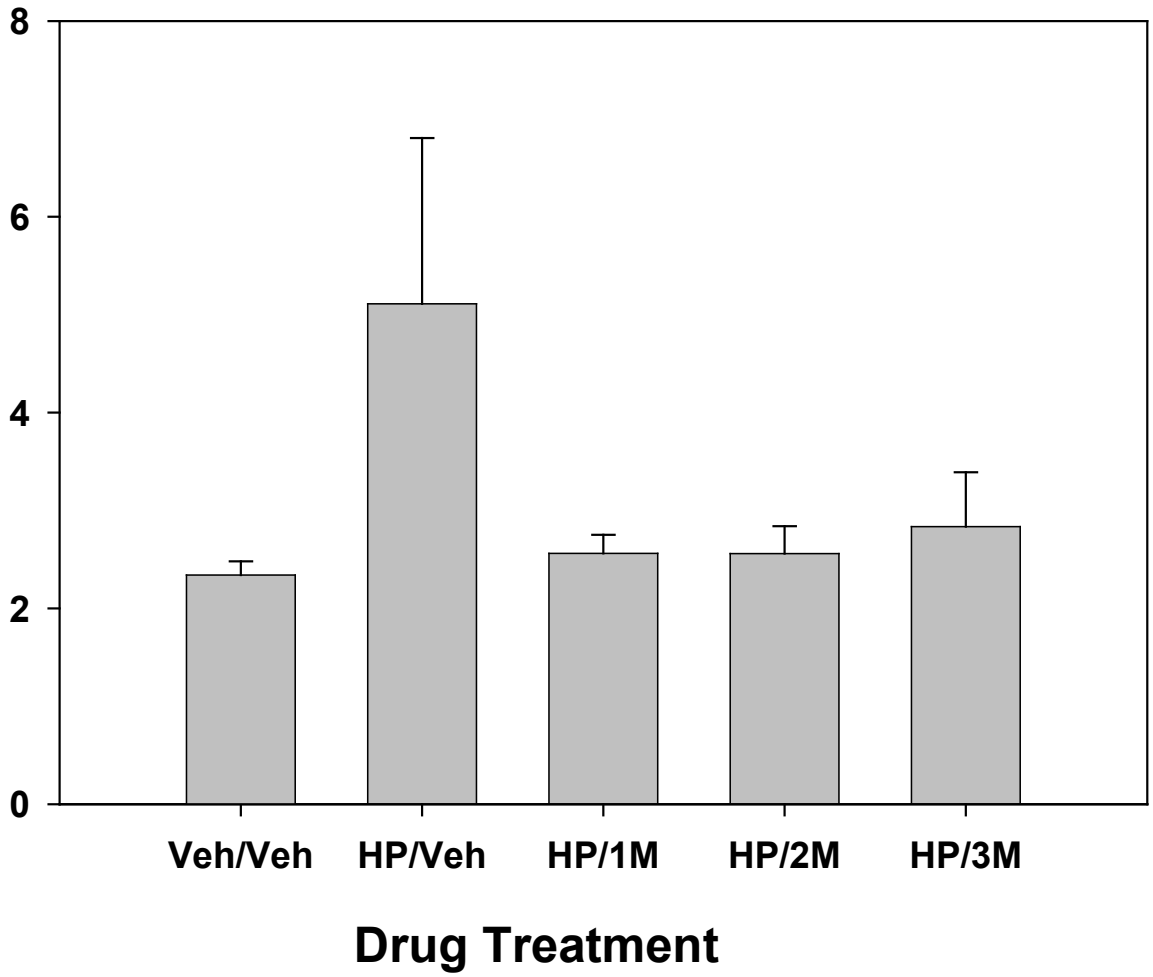


Fig. 4.2. Effects of the adenosine A2A specific antagonist, MSX-3, on T-maze run latency in mice. Mean (±SEM) run latency (average in seconds across 30 trials) after IP treatment with vehicle (Veh) or haloperidol (HP, 0.1mg/kg, 50 minutes before test) plus various doses of MSX-3 (M; 1.0, 2.0 and 3.0 mg/kg, 20 minutes before test) are shown.

## CONCLUSIONS:

In the present studies, a T-maze paradigm was used to characterize the effects of the DA D2 receptor antagonist haloperidol, and to examine the interaction between haloperidol and adenosine antagonists. The results with the T-maze barrier task are in accordance with results found with the operant procedures in rats (Salamone et al., 1991, 1992, 1996, 2002, 2008, 2009; Cousins et al., 1993; 1994; Cousins and Salamone 1994; Koch et al. 2000; Sink et al. 2008; Farrar et al.2007, Worden et al. 2008). Control animals strongly prefer to climb the barrier to obtain the high density of food. D2 antagonism altered the HD arm selection redirecting the behavior towards the less demanding response option.

Theophylline, a nonselective adenosine antagonist, could partially reverse the effects of haloperidol (0.1 mg/kg) on the T-maze barrier choice paradigm. Theophylline produced a moderate improvement in the selection of the HD arm in haloperidol treated animals at the two highest doses (10 and 15 mg/kg). Mice redirected their behavior to the HD arm, although not reaching veh/veh levels. Latency to reach the food was unaffected after haloperidol plus theophylline treatment. The effects of theophylline on the T-maze choice impairment induced by haloperidol are similar to the effects of another nonselective adenosine antagonist in the concurrent chow/FR5 schedule operant task (Salamone et al., 2009). Caffeine was able to reverse haloperidol effects, but its effect size was smaller than the effect of an A2A antagonist (KW6002) but bigger than that produced by an A1 antagonist (DPCPX; Salamone et al., 2009).

Co-administration of adenosine A2A antagonist MSX-3 with haloperidol restored the behavior towards the highest demanding response option; mice selected to climb the barrier on nearly all of the trials. These results were obtained with the two highest doses of MSX-3 used (2.0 and 3.0 mg/kg), which reached HD choice levels comparable to the veh/veh control group. Only the lowest dose MSX-3 used failed to reverse the haloperidol effects. On latency to reach the food these treatments did not produce any significant effect. Previous studies with rats on a T-maze and in the operant box using MSX-3 and DA D2 antagonists showed the same pattern of results (Mott et al., 2009; Farrar et al., 2007, Worden et al., 2008). All these data together demonstrate that A2A antagonism can reverse D2 antagonism on a task where an effort-related process is evaluated.

In summary, present and previous results are seen as consistent with the suggestion that DA antagonism alters choice behavior on tasks in which different response options involve different effort requirements. Thus, DA antagonists and accumbens DA depletions can be altering behavioral activation, instrumental response output, response allocation, or effort-related processes (Salamone et al., 2008).

As an increasing body of literature emerges detailing the motivational functions of DA, and the possible interactions between DA and adenosine, several clinical applications should also be recognized. The role of DA is well established in such clinical disorders such as schizophrenia and Parkinson's disease. However DA also is implicated in aspects of depression, including such fundamental symptoms as feelings of listlessness, decreased energy levels and fatigue (Stahl, 2002), and it had been suggested that the biological basis of fatigue, energy and motivational impairments found in depression are unknown (Stahl, 2002). As D2 antagonism induces motor impairments as well as motivational impairments in effort related choice procedures, it has been suggested that psychomotor slowing in depression may be functionally similar to the impairment in activational aspects of motivation that results from a suppression of DA activity in the brain (Salamone et al., 2007).

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