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Synergistic effects of dopamine D2-like receptor antagonist sulpiride and beta-blocker propranolol on learning in the Carousel maze, a dry-land spatial navigation task☆

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ABSTRACT

Spatial navigation attracts the attention of neuroscientists as an animal analogue of human declarative memory. The Carousel maze is a dry-land navigational paradigm, which proved to be useful in studying neurobiological substrates of learning. The task involves avoidance of a stable sector on a rotating arena and is highly dependent upon the hippocampus. The present study aims at testing hypothesis that sulpiride (a centrally-active dopamine D2-like receptor antagonist) and propranolol (a beta-blocker) impair spatial learning in the Carousel maze after combined systemic administration. These doses were previously shown to be sub-threshold in this task. Results showed that both substances affected behavior and significantly potentiated their negative effects on spatial learning. This suggests central interaction of both types of receptors in influencing acquisition of this dynamic-environment task.

1. Introduction

Spatial navigation, a model of declarative memory (O´Keefe and Nadel, 1978), is of immense interest for cognitive neuroscientists. Almost 15 years ago, active allothetic place avoidance task (AAPA) was designed (Bures et al., 1997; Stuchlik et al., 2001), referred here to as the Carousel maze. Rats are trained to avoid a sector that is stable in the coordinate frame of the room on a continuously rotating arena (Stuchlik et al., 2004). The task requires spatial navigation (Bures et al., 1997; Cimadevilla et al., 2001) and cognitive coordination and selection of appropriate behavioral strategy to manage efficient performance (Wesierska et al., 2005; Dockery and Wesierska, 2010). Moreover, inertial cues generated by rotation are necessary for acquisition of the test (Blahna et al., 2011). The Carousel maze performance depends upon the hippocampus, with even unilateral hippocampal inactivation having deleterious effect (Cimadevilla et al., 2001). In recent studies, Carousel maze was used to evaluate the neuropharmacological effects upon behavior (Vales et al., 2006; Bubenikova-Valesova et al., 2008; Stuchlik et al., 2009; Petrasek et al., 2010). Moreover, consequences of lesions (Svoboda et al., 2008; Wesierska et al., 2009) as well as other experimental manipulations (Wesierska et al., 2006) were tested in this behavioral paradigm.

Noradrenaline plays a role in many brain functions including learning and memory. Most of noradrenergic neurons originate in A1–A7 brainstem nuclei (including the *locus coeruleus*) and innervate areas including those related to cognition (hippocampus, septum and neocortex) (Géranton et al., 2003). Two superfamilies of noradrenergic receptors – named alpha and beta – are distinguished (for review see Smythies, 2005). Adrenoceptors in the brain mediate mainly the central effects of noradrenaline. Regarding memory, beta-adrenoceptors are studied more deeply than alpha-adrenoceptors (Przybyslawski et al., 1999). Propranolol, a centrally active antagonist of beta-adrenoceptors is mostly used for studying memory consolidation and reconsolidation (Przybyslawski et al., 1999; Cahill et al., 2000). Dose-dependent effects of propranolol administered before learning in the Carousel maze were shown by our previous study (Stuchlik et al., 2009). It reported a disruption of place avoidance learning, while preserving intact locomotor activity to some extent; however, a high dose (30 mg/kg) caused marked sedation. Adverse effect of this drug was demonstrated in a motor task (Heron et al., 1996), suggesting the effects of propranolol were not restricted to the spatial domain.

Dopaminergic neurons form pathways, generally divided into four systems (nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular). Dopamine in the hippocampus releases from fibers originating in the ventral tegmental area (Berger et al., 1985; Verney et al., 1985), some

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fibers in the dorsal hippocampus originate in the *substantia nigra*. Dopaminergic D2-like receptors may mediate the effect of dopamine on mnemonic functions and can be associated with spatial learning and long-term potentiation (LTP) during memory consolidation (Fujishiro et al., 2005). The prefrontal cortex, a brain structure with a vast proportion of dopaminergic fibers and terminals (Verney et al., 1985), is a crucial region for cognitive and attention processes associated with executive functions.

The effect of specific receptor antagonists on spatial learning and navigation belongs to intensively studied topics today (for review see Myhrer, 2003). Notably, it is worth pointing out that both drugs have been extensively prescribed in clinical practice; sulpiride is an atypical antipsychotic drug and propranolol was used for treatment of cardiovascular disorders, despite its limited usage today. The present study aimed at revealing possible interaction between beta-adrenoceptors and D2-like receptors in the regulation of locomotion and learning in the Carousel maze. We administered non-selective beta-receptor antagonist propranolol and D2-like receptor antagonist sulpiride prior to acquisition sessions and hypothesized that co-application of both drugs would impair avoidance at the doses, which had caused minor or no impairments when administered independently in previous studies (Stuchlik et al., 2007a,b, 2009). The study therefore aimed at acute effects of both drugs either applied separately or in combination.

2. Methods

2.1. Animals

Experimental manipulations complied with the Animal Protection Code of Czech Republic and EU directive 86/609/EEC. Sixty-nine naive male Long–Evans rats (12–14 weeks old, 250–300 g), obtained from breeding colony of the Institute of Physiology, were housed in pairs in 30×30×40-cm translucent cages in an air-conditioned facility with a stable temperature and 12/12 light/dark cycle (lights on at 7.00). Conscious rats were gently implanted with a hypodermic needle, piercing the rat's skin between its shoulders, and creating a small loop on the needle with tweezers. The loop prevented the needle from slipping out and provided purchase for an alligator clip, which was connected a shock-delivering cable, used in behavioral testing. Water and food was freely available.

2.2. Drugs

Propranolol (propranolol HCl; SigmaAldrich, Czech Republic) was dissolved in distilled water at concentrations of 5 and 20 mg/ml and injected intraperitoneally 20 min prior to each session at doses 5 and 20 mg/kg. Saline (1 ml/kg) was injected as a control for propranolol injection. Sulpiride (SigmaAldrich, Czech Republic; 5 and 30 mg/ml) was dissolved in a drop of glacial acetic acid, and diluted into a total volume with a 5% solution of glucose. A control condition to sulpiride injection consisted of a blank solution with all components of the vehicle but without an active substance (sulpiride vehicle). Sulpiride and sulpiride vehicle were injected subcutaneously at volume of 1 ml/kg 40 min prior to each session.

2.3. Design of experiments

The study was designed to assess the effect of combined application sulpiride and propranolol. Effects of drugs were reported for the final two days of the 4-day-acquition block in the Carousel Maze which represented asymptotic performance. Nine groups were used. Animals were injected with saline (1 ml/kg) + the sulpiride vehicle (1 mg/kg; $n=8$; control group), propranolol 5 mg/kg (n = 7) and 20 mg/kg (n = 8) + sulpiride vehicle, or sulpiride (5 mg/kg and 30 mg/kg) + saline ($n=6, 8$; respectively). Animals treated with combination of drugs obtained 5 mg/kg of propranolol + 5 mg/kg sulpiride ($n=8$), 5 mg/kg propranolol + 30 mg/kg of sulpiride ($n=8$), 20 mg/kg propranolol + 5 mg/kg sulpiride ($n=8$) and 20 mg/kg propranolol + 30 mg/kg sulpiride ($n=8$). A control group obtained intraperitoneal injection of 1 mg/ml saline 20 min prior to learning sessions and subcutaneous injection of sulpiride vehicle 40 min prior to testing. The doses were selected as subthreshold on the basis of our previous studies (Stuchlik et al., 2007a,b; Stuchlik et al., 2009).

2.4. Behavioral apparatus and experimental procedure

The Carousel maze apparatus (Cimadevilla et al., 2000; Stuchlik and Vales, 2005) consisted of a metallic circular arena (82 cm in diameter) enclosed by a 30-cm transparent Plexiglas wall; constantly rotating clockwise at one revolution per minute. The arena was elevated 1 m above the floor of a room containing many extramaze cues. A light-emitting diode (LED) located on the arena circumference monitored arena rotation, another LED was mounted on a small jacket worn by a rat and signaled its position. At the beginning of each session, a rat was placed onto the rotating arena to a place directly opposite to the to-be-avoided sector. A PC-based tracking system (iTrack; Biosignal Group) in an adjacent room recorded the position of the rat. Data were stored for off-line analysis (TrackAnalysis; Biosignal Group). A 60-deg sector was defined by its relationships to room cues. It remained in a stable spatial position throughout the training. Whenever the rat entered it for more than 500 ms, the tracking system delivered a mild, constant-current shock (AC; 50 Hz, 0.5 s, 0.3–0.7 mA). The current was individualized for each rat to elicit a rapid escape response but to prevent freezing. In most cases, animals responded to 0.4 mA. If a rat did not leave the sector, additional shocks were given every 1200 ms, but no more entrances were counted until the rat left the sector for more than 300 ms. Shocks were delivered through the implanted needle and the arena floor. The procedure has been previously described to be efficient and safe for the rats (Stuchlik et al., 2004; Wesierska et al., 2005; Blahna et al., 2011). After each rat, the arena floor was cleaned with detergent, ensuring the rats could not use inter-trial scent marks.

2.5. Evaluated parameters and statistical analysis

Four daily 20-min sessions in the Carousel maze were conducted between 9.00 and 13.00. Entrances into the sector were punished throughout the training. The following parameters were extracted from the tracks: The ***total distance*** per session reflected the active locomotor activity of animals (Stuchlik et al., 2004) and was measured by a sum of distances of point sampled every 1 s in the coordinate frame of the arena. Two measures of spatial learning were the ***number of errors*** (number of entrances into the sector) and maximum time between two entrances (***maximum time avoided***). Latency to the first entrance in a session (***time of first error***) was a measure of between-session learning. Number of errors and time of first error were positively skewed; we used logarithmic transformation to make their distributions closer to normal. Before doing so, we added a constant 1 to these measures to ascertain that the minimum value was not lower than one. Subsequent analyses for these measures were computed using the transformed data. Animals showed stable performance by the third day of the experiment; therefore, we used the last two days for analysis. In order to combine these two days, standard scores were computed for each day and variable. Then, the average of standard scores for the third and fourth day was computed for each measure. Finally, standard scores for these averages were computed to simplify interpretation. All transformations were done prior to data submission into statistical analysis. The procedure was described in detail elsewhere (Quinn and Keough, 2002). Median values of the final session's performance are shown in Table 1. We used the last two sessions for analysis, despite the effect of the drugs could occur from the initial sessions. However, we did not observe such effects (data not shown).

Table 1
The table shows the median values of selected parameters of performance in the final session of testing for all groups. We present medians instead of means due to non-normal distribution of the raw data. Note the decrease of the total distance after co-application of higher doses of propranolol. The values of errors were increased and the values of maximum time avoided decreased after co-application of both doses.

Propranolol	Sulpiride	Distance Day 4	Errors Day 4	Time to first error Day 4	Max. time avoided Day 4
Saline	Vehicle	61.7	2.5	191.4	587.0
5 mg/kg	Vehicle	60.0	3.0	121.2	577.0
20 mg/kg	Vehicle	50.1	2.0	100.9	892.5
Saline	5 mg/kg	59.5	5.0	41.6	449.5
5 mg/kg	5 mg/kg	68.6	20.5	72.7	140.0
20 mg/kg	5 mg/kg	32.5	23.5	71.0	110.5
Saline	30 mg/kg	66.7	3.0	172.5	616.5
5 mg/kg	30 mg/kg	52.0	11.0	76.5	580.0
20 mg/kg	30 mg/kg	41.2	18.0	85.7	162.5

The resultant variables were used for a two-way analysis of variance. Doses of propranolol and sulpiride served as between-subject factors. Since we aimed at a synergistic effect of propranolol and sulpiride, we used Helmert planned contrasts. Helmert contrasts compare each level of a factor with the mean effect of subsequent levels. In our experiment, it means that within each factor the effect of an application of a drug (which is the comparison of saline/vehicle against both doses of a respective drug) and the effect of a dose of a drug (which is the comparison of small and large dose) were tested. The synergistic effect was tested by the effect of interaction between application of propranolol and application of sulpiride. It should be noted that the used measures were correlated and the results of statistical tests are therefore not independent. Maximum time avoided and number of errors correlated highly ($r = -0.92$); all other intercorrelations were in the range of $0.45 < |r| < 0.60$ with the only exception of the correlation between total distance and time to first error ($r = 0.13$). Only correlations with number of errors were negative. Note that for simplicity, we use original parameter labels (such as total distance, number of error, etc.) throughout Section 3 and in the figure; however, all analyses were done on the variables computed by the method described in this section.

All reported p-values are for two-tailed significance tests. Since one-tailed tests are often used when planned contrasts are applied, significance values reported in the present article are rather conservative. We report as marginally significant the results that would be significant when using one-tailed tests. Effect sizes are reported with use of $r_{effect\ size}$, which is a correlation between observed data and regression weights for a given contrast. Positive values indicate that the correlation was in the predicted direction. Squared value of $r_{effect\ size}$ can be interpreted as the proportion of variance explained by the contrast (Furr, 2004).

3. Results

Example trajectories of typical rats from selected groups are depicted in Fig. 1. First, we inspected the effects of drugs on locomotion measured by total distance walked in a session. Planned contrasts for total distance showed significant effect of propranolol application, $t(60) = 3.32$, $p = 0.002$, $r_{effect\ size} = 0.39$; marginally significant effect of propranolol dose, $t(60) = 1.74$, $p = 0.09$, $r_{effect\ size} = 0.19$; and marginally significant effect of sulpiride application, $t(60) = 1.83$, $p = 0.07$, $r_{effect\ size} = 0.21$. This means that the application of propranolol decreased total distance traversed by the animals and there was an indication that this effect was dose-dependent. The application of sulpiride had similar effect but there was no indication of dose-dependency of the effect. The effect of the interaction between propranolol and sulpiride application was not significant; however, there was a trend in the predicted direction $t(60) = 1.60$, $p = 0.12$, $r_{effect\ size} = 0.17$ (Fig. 2). The statistical analysis did not allow for comparison between control group and propranolol (or sulpiride) alone; however, the significant main effect of the drug could be at least in part attributed to co-application of both drugs (see Petrasek et al., 2010; Stuchlik et al., 2008).

Subsequently, we evaluated the spatial parameters. Planned contrasts for number of errors revealed significant effect of propranolol

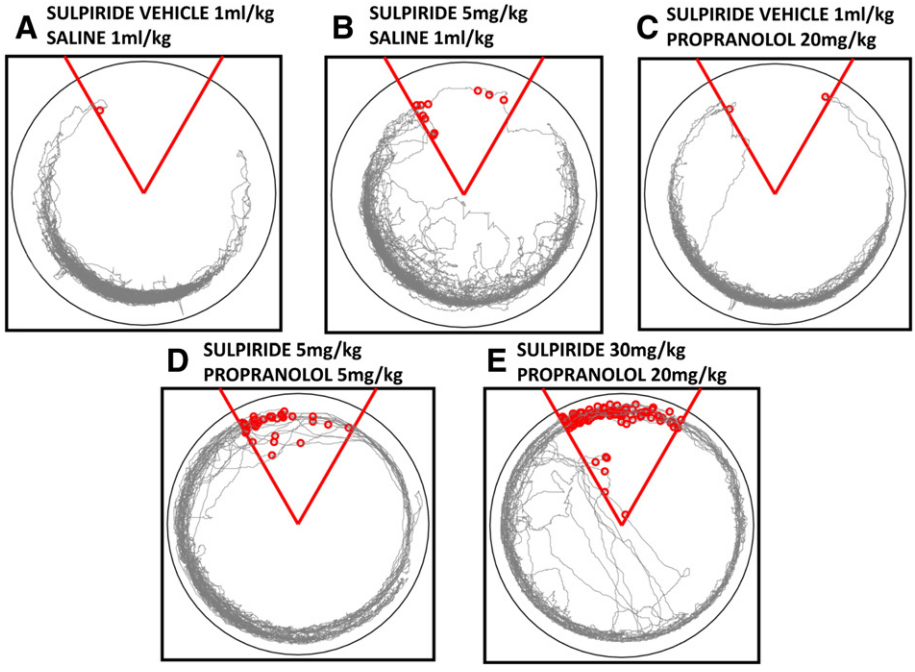

Fig. 1. Representative trajectories of animals from selected experimental groups. ***Panel A*** shows a control rat (treated only with saline and sulpiride vehicle), which was capable of efficient avoidance. ***Panels B and C*** show animals treated with sulpiride and propranolol, respectively (plus control vehicle injections); both showing spared avoidance. ***Panel D*** shows a track of animal treated with 5 mg/kg sulpiride plus 5 mg/kg of propranolol, showing impaired avoidance, but normal locomotion. ***Panel E*** shows a trajectory of an animal co-applied with higher doses of the above-mentioned drugs, exhibiting severe avoidance and procedural deficit. The trajectories are depicted in grey; small circles denoted places of shocks.

application, $t(60) = 2.80$, $p = 0.007$, $r_{effect\ size} = 0.32$; significant effect of sulpiride application, $t(60) = 3.05$, $p = 0.003$, $r_{effect\ size} = 0.35$. Both propranolol and sulpiride application increased number of errors in the task; however, the effect of drugs did not seem to be dependent on applied dose. The effect of the interaction between propranolol and sulpiride application was not significant; however, there was a trend in the predicted direction $t(60) = 1.48$, $p = 0.14$, $r_{effect\ size} = 0.16$ (Fig. 2).

The evaluation of maximum time avoided showed significant effect of propranolol application, $t(60) = 2.02$, $p = 0.048$, $r_{effect\ size} = 0.23$; significant effect of sulpiride application, $t(60) = 2.91$, $p = 0.005$, $r_{effect\ size} = 0.34$; significant effect of the interaction between propranolol and sulpiride application, $t(60) = 2.13$, $p = 0.037$, $r_{effect\ size} = 0.24$; and marginally significant effect of the interaction between propranolol dose and sulpiride application, $t(60) = 1.72$, $p = 0.09$, $r_{effect\ size} = 0.20$. The results therefore showed reduction in maximum time avoided by application of both propranolol and sulpiride and this effect was pronounced by concurrent application of both drugs, proving synergism of their effects (Fig. 2). Again, the main effects of the drug application could be partially ascribed to co-application of the drugs. Similarly to previous parameters, direct comparison was not accessible using the current statistical design.

Finally, we evaluated between-session learning, provided by the time to first entrance into the to-be-avoided sector. Planned contrasts for time to first error did not reveal any significant effect (Fig. 2). This might be due to relatively lower reliability of this parameter expressed as low correlations between its values in particular daily sessions.

4. Discussion

The present study showed acute effects of administration of propranolol and sulpiride on locomotor activity and spatial learning in the Carousel maze, when both drugs were administered prior to daily testing. More importantly, results demonstrated an interaction between acute systemic administration of dopamine D2 receptor antagonist sulpiride and beta-adrenoceptor antagonist propranolol in influencing spatial learning. Simultaneous application of both drugs

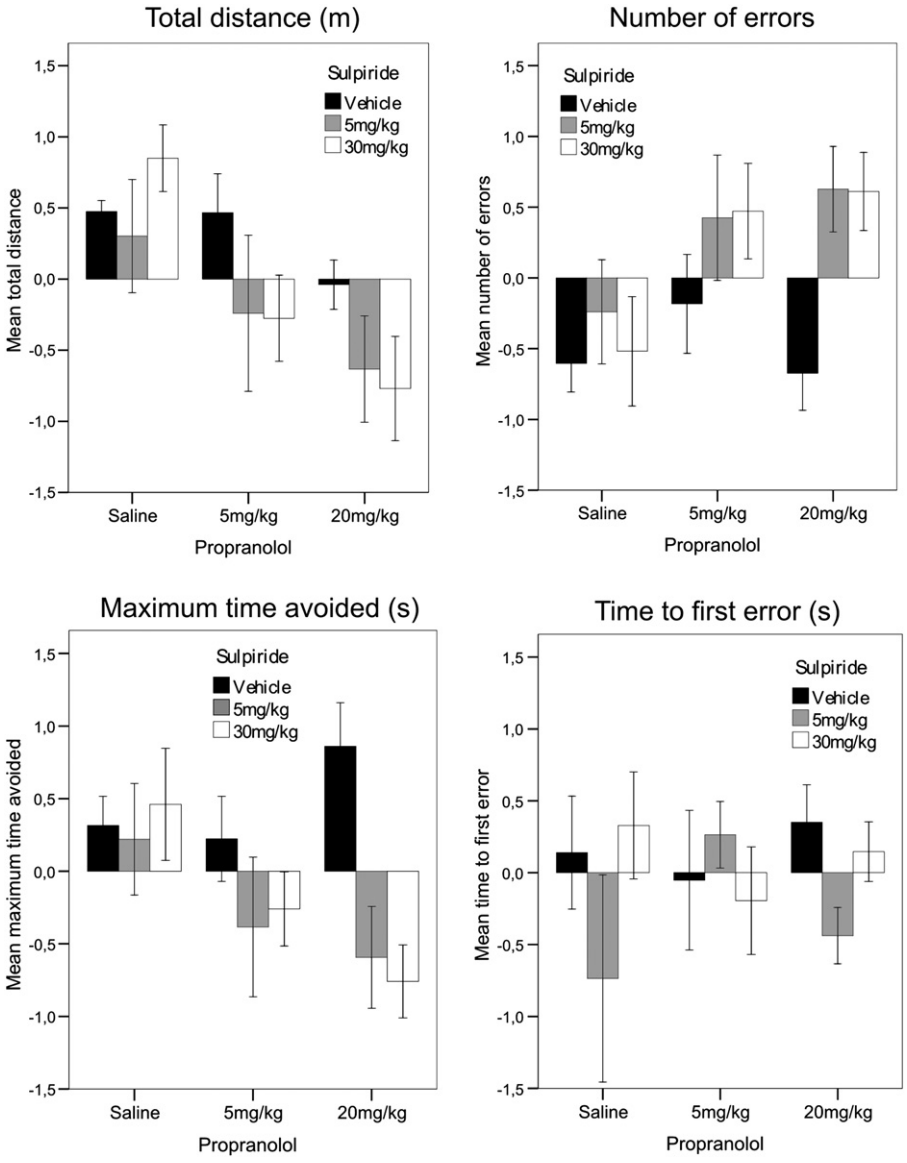

Fig. 2. Graphs show mean (±S.E.M.) standardized scores for measures of performance (total distance, number of errors, maximum time avoided and time to first error) in the Carousel maze. The standard scores were computed from the average of standardized data of the last two days of experiment representing asymptotic performance. Data for number of errors and maximum time avoided were logarithmically transformed before the first standardization. The values of means on graphs represent how many standard deviations is the mean of a group above the grand mean. The potentiation of drug effects can be seen as the difference in direction of means for groups with drug co-application and groups without both drugs applied.

resulted in larger decrement in performance than would be expected if the effects of drugs were additive, showing a potentiation of effects of both drugs on the spatial avoidance parameters. While it was significant only for maximum time avoided measure, there was a non-significant trend in the predicted direction for both total distance and number of errors, which further supports confidence of our result.

The observed synergistic effects of sulpiride and propranolol suggest, in general terms, an interaction between dopamine D2-like and beta-adrenergic receptors on the systemic level. Our results add to previous studies aimed at elucidating this interaction using peripheral or intracerebral application of specific receptor antagonists. For instance, Lalumiere et al. (2004) infused sulpiride into the basolateral amygdala (BLA) immediately post-training of inhibitory avoidance task and detected a memory retention impairment. Moreover, beta-adrenergic receptor antagonists co-infused into the BLA together with dopamine blocked the memory enhancing effects of dopamine. These findings indicated that dopaminergic activation within the BLA modulates memory consolidation and that this modulation involves concurrent activation of beta-adrenergic and dopamine influences within this brain region. However, the study also suggested an existence of brain regions where dopamine effects on memory do not require concurrent activation of beta-adrenergic receptors. This might perhaps explain conclusions of the study performed by Williams et al. (1994), in which propranolol injections did not block the amphetamine-induced memory enhancement and the experiment, in which post-training systemic administration of a dopamine-beta-hydroxylase inhibitor diethyldithiocarbamate (increasing brain dopamine but decreasing noradrenaline levels) enhanced memory retention (Haycock et al., 1976).

However, when comparing our results to other studies on this topic, one must keep aware of serious constraint represented by difference between pre- and post-training application (aimed at memory encoding and consolidation, respectively). The issue of possible consolidation of the Carousel maze memory trace has not been fully elucidated yet (but see Vafaei et al., 2007); however, our previous study showed that pre-test administration of 10 mg/kg propranolol did not disturb either subsequent performance or latency to first error in the next session (24.5 h later). The latter finding could be interpreted as that consolidation of place avoidance memory did not require beta-adrenoceptors (Stuchlik et al., 2009). The present study shows that both drugs can potentiate their effects on acquisition of spatial learning task when applied *before* behavioral procedure and together with previous studies suggest that this effect could be ascribed mainly to acute effects of the drugs instead of modulating memory consolidation.

On the other hand, some studies failed to show an acute interaction of dopamine D2-like and beta-noradrenergic receptors. Anisman et al. (1981) reported reduction of haloperidol-induced deficits in escape behavior by alpha-adrenergic receptor blocker; nonetheless, the study failed to show an effect of propranolol. A specific modulation of stress-induced activation of subcortical dopaminergic transmission by noradrenaline input to prefrontal cortex acting at alpha1-receptors was described (Nicniocaill and Gratton, 2007), but again, with no significant effect of beta1/2-adrenoceptor blockade by alprenolol. Moreover, consequences of locally-applied dopamine on noradrenaline in the PFC were reported to be attenuated by local D1-like receptor (SCH23390) but not D2-like receptor blockade (sulpiride). This may suggest that PFC is not the crucial region where interaction observed in the present study occurs.

Recently, we have shown a synergistic interaction between D2-like receptor antagonist sulpiride and alpha1-blocker prazosin, which impaired both locomotor activity and navigation efficiency in the Carousel maze when co-applied (Stuchlik et al., 2008). Disruption of learning in the same task after combined systemic administration of low doses of beta- and alpha-blockers propranolol and prazosin was reported too (Petrasek et al., 2010). Since there is recent evidence for interaction between dopamine and noradrenaline neurotransmitter systems in the hippocampus (Borgkvist et al., 2011), it is conceivable that *in vivo* synergism between these two systems may exist in the hippocampus locally on the receptor or synaptic level.

Possible non-specific effects of sulpiride and propranolol on behavior or influences on cardiovascular system or perception of shocks may have hypothetically interfered with successful avoidance. Such possibility could not be absolutely excluded with the present study; however, preferential influence upon spatial parameters and escape reactions performed from the sector suggest that this was not the case. A previous study (Stuchlik et al., 2009) revealed that rats treated with doses of propranolol as high as 20 mg/kg exerted normal locomotion in the arena, despite effects of the drug on blood pressure (Singh et al., 1990). Moreover, administration of sulpiride doses up to 100 mg/kg was found not to affect navigation to visible platform in the water maze, suggesting intact procedural functions (Stuchlik et al., 2007b). It should be, however, pointed out that the locomotion in the Carousel maze can be viewed as 'forced' activity instead of spontaneous ambulation such as in the open-field test. Nonetheless, a more detailed investigation of systemic effects of drugs would be highly helpful in elucidation of contribution by central vs. peripheral mechanisms.

5. Conclusions

We found that propranolol (5 and 20 mg/kg) and sulpiride (5 and 30 mg/kg) affected locomotion and acquisition of spatial avoidance behavior in the Carousel maze. Moreover, results of the present study show that in the Carousel maze, an aversive navigational task with high hippocampal demand, systemic co-application of beta-adrenergic and dopamine D2 antagonists, propranolol and sulpiride, respectively, significantly potentiated their adverse effects on spatial performance of the animals. This suggests an interaction between dopamine and noradrenergic systems in encoding a memory trace in a dry-land spatial navigation task.

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