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O PAPEL DOS ANTIPSICÓTICOS CLOZAPINA, OLANZAPINA E RISPERIDONA NA ORIENTAÇÃO ESPACIAL EGOCÊNTRICA EM RATOS

CIBELE CANAL CASTRO

Orientador: Prof. Iván Izquierdo
Co-Orientador: Prof. Werner J. Schmidt

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SUMÁRIO

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RESUMO

Ratos machos *Long-Evans* e *Wistar* foram submetidos a uma tarefa de alternância de escolhas num labirinto em Y (delayed two-alternative-choice task). Esta tarefa requer orientação espacial egocêntrica (baseada na localização do animal dentro do aparelho) e, ao mesmo tempo, exclui a orientação espacial alocêntrica (baseada na detecção de elementos visuais externos ao aparelho).

Os animais foram expostos a 10 sessões de treino para cada animal, os quais eram submetidos a injeção de salina (controles), ou dos antipsicóticos clozapina (0,5 ,g/kg i.m.), olanzapina (0,5 mg/kg i.p.) e risperidona (0,5 mg/kg i.p.) uma hora antes do início de cada tarefa. Na primeira sessão, os ratos eram recompensados por seguir até o final de cada braço, onde achavam comida. Nas seguintes nove corridas, os animais eram recompensados somente se eles entrassem no braço que não tinha sido previamente escolhido. Mediu-se também o tempo de corrida até o final de cada braço, com o consumo da comida. Um tempo limite foi estabelecido para esse tempo: se em 180 segundos o animal não consumasse a tarefa, o mesmo era retirado do aparelho e colocado no braço inicial. Com o objetivo de excluir orientação espacial alocêntrica (ou seja, utilizando sinais externos ao aparelho), a orientação do Y-maze foi modificada dia após dia, em uma ordem pseudo-randomizada. A tarefa foi desenvolvida em dias consecutivos, sem pausa.

Os resultados dos experimentos demonstraram que os antipsicóticos clozapina e olanzapina prejudicaram a orientação espacial egocêntrica no labirinto em Y. Em contrapartida, risperidona prejudicou a orientação espacial egocêntrica somente nos primeiros quatro dias; nos seguintes quatro dias não teve nenhum efeito. O tempo de corrida não foi alterado pela clozapina e foi prolongado pela olanzapina e pela

risperidona. Não se observou catalepsia ou redução do comportamento cognitivo; nos animais tratados com olanzapina observou-se uma leve sedação.

ABSTRACT

Many studies indicate a dissociation between two forms of orientation: Allocentric orientation, in which an organism orients on the basis of cues external to the organism, and egocentric spatial orientation (ESO) by which an organism orients on the basis of proprioceptive information. While allocentric orientation is mediated primarily by the hippocampus and its afferent and efferent connections, ESO is mediated by the prefronto-striatal system. Striatal lesions as well as classical neuroleptics, which block dopamine receptors, act through the prefronto-striatal system and impair ESO. The purpose of the present study was to determine the effects of the atypical antipsychotics clozapine (0,5 mg/kg i.m.), olanzapine (0,5 mg/kg i.p.) and risperidone (0,5 mg/kg i.p) which are believed to exert its antipsychotic effects mainly by dopaminergic, cholinergic and serotonergic mechanisms. A delayed-two-alternative-choice-task, under conditions that required ESO and at the same time excluded allocentric spatial orientation was used. Clozapine (and olanzapine treated rats made more errors than risperidone treated rats in the delayed alternation in comparison with the controls. Motor abilities were not impaired by any of the drugs. Thus, with regard to the delayed alternation requiring ESO, clozapine and olanzapine but not risperidone may be considered to act probably by affecting the prefronto-striatal system in a similar way to classical neuroleptics.

INTRODUÇÃO

A memória de trabalho processa e conserva informações enquanto esta está sendo percebida e/ou adquirida, e por alguns poucos segundos ou minutos depois; seu papel é fazer com que as experiências possam ser entendidas, reconhecidas como novas ou não, e depois eventualmente armazenadas (Baddeley, 1986; Goldman-Rakic, 1996). A memória de trabalho depende da atividade elétrica do córtex pré-frontal antero-lateral e áreas vizinhas (Goldman-Rakic, 1996; Salmon et al., 1996). Esta região tem conexões aferentes e aferentes com o córtex entorrinal e, através dela, com o hipocampo, amígdala, córtex parietal e córtex cingulado (Izquierdo, 2002). No processamento da memória de trabalho e no seu cotejo com memórias preexistentes ou que estão sendo evocadas ou formadas, intervêm todas essas conexões (Goldman-Rakic, 1996; Izquierdo et al., 1998; Izquierdo, 2002). Por outro lado, o córtex pre-frontal também tem conexões de ida e volta com o striatum através de neurônios que se intercomunicam. Mais especificamente, o striatum projeta seus neurônios até o medial palidum, que por sua vez projeta suas vias neuronais até o tálamo, que tem conexões com áreas pré-límbicas e infralímbicas. (Ragozzino, Kesner and Mizumori, 2002).

Tem sido sugerido que a informação espacial é organizada dentro de dois mapas cognitivos diferentes: um mapa **egocêntrico**, baseado na orientação do corpo em relação ao espaço onde ele se encontra (eg., o aparelho de treino); e um mapa **alocêntrico,** em que o processamento de informação é baseado em estímulos visuais ou olfatórios distantes (eg., “dicas” nas paredes da sala em que o aparelho de treino

se encontra) (Kesner, Farnsworth and DiMattia, 1989; Dietrich and Schmidt, 2002). Portanto, entende-se por **orientação espacial alocêntrica (OEA)**, quando um organismo se baseia em pistas externas ao local do treino, e por **orientação espacial egocêntrica (OEE)** a dependente de informações proprioceptivas ou visualmente muito próximas. Enquanto a OEA é mediada primariamente pelo hipocampo e suas conexões aferentes e eferentes, a OEE é mediada pelo sistema pré fronto-striatal (Cook and Kesner, 1988; Ragozzino and Kesner, 2001).

Os fármacos antipsicóticos tradicionais (clorpromazina, haloperidol, etc.), que bloqueiam receptores dopaminérgicos e que atuam através do sistema pré fronto-striatal, podem prejudicar a OEE, já que o sistema dopaminérgico parece ser importante para a manutenção da memória de trabalho (Aujla and Beninger, 2001). Estes fármacos, porém, tem como inconveniente a indução de sintomas de dano extrapiramidal, como disquinesias tardias e outros.

A clozapina, a olanzapina e a risperidona são antipsicóticos atípicos, que representam uma geração mais recente dentro dessa família, que permitem o tratamento da esquizofrenia com uma incidência muito menor de sintomas extrapiramidais residuais. Esse perfil do efeito colateral mais benigno dos novos antipsicóticos tem sido atribuído a ações sobre sinapses cujo neurotransmissor é a serotonina (5HT). A literatura mais atual atribui essas ações a um antagonismo dos receptores 5-HT_{2A} em poder atenuar os efeitos dopaminérgicos bloqueadores desses antipsicóticos, deste modo diminuindo os efeitos extrapiramidais que os clássicos neurolépticos produzem quando administrados (Rosengarten and Quartermain, 2002).

A clozapina foi o primeiro destes modernos antipsicóticos a ser introduzido (Buchanan et al., 1998; Buckley, 1999). Interage com alta ou moderada afinidade com receptores serotonérgicos (5-HT_{2A}, 5-HT_{2C} e outros), receptores colinérgicos muscarínicos, adrenérgicos (α_1, α_2, β_2), histamínicos H_1; mas também tem alta afinidade por receptores dopaminérgicos D_4. Posteriormente surgiram a olanzapina e

a risperidona, que atuam no sistema serotonérgico através de receptores 5-HT_{2A} e no sistema dopaminérgico através dos receptores dopaminérgicos D_2 (Bymaster et al., 1996; Schotte et al., 1996; Gunasekara and Spencer, 1998).

Tendo em vista a alta eficácia desses agentes em reduzir os sintomas da esquizofrenia e sua reduzida probabilidade de efeitos colaterais motores, o presente estudo teve como objetivo examinar os efeitos dos antipsicóticos clozapina (0,5 mg/kg i.m.), olanzapina (0,5 mg/kg i.p.) e risperidona (0,5 mg/kg i.p.) sobre uma tarefa que requer orientação espacial egocêntrica. Tal tarefa foi testada por um sistema de alternância de escolhas num labirinto em Y ("delayed two-alternative-choice") sob condições que requerem OEE e, ao mesmo tempo, excluem OEA (Dietrich and Schmidt, 2002).

Clozapine, Olanzapine but not Risperidone impairs egocentric spatial orientation in a delayed-two-alternative-choice-task

C. C. Castro, W. J. Schmidt, I. Izquierdo

Centro de Memória, Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos 2600, 90035-003 Porto Alegre, RS, Brazil; University of Tübingen Zoological Institute, Departament of Neuropharmacology, Mohlstrasse 54/1, 72076 Tübingen, Germany

Correspondence to Cibele C. Castro, Centro de Memória, Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos 2600, 90035-003 Porto Alegre, RS, Brazil. E-mail: cibele.castro@terra.com.br

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Abstract

Many studies indicate a dissociation between two forms of orientation: Allocentric orientation, in which an organism orients on the basis of cues external to the organism, and egocentric spatial orientation (ESO) by which an organism orients on the basis of proprioceptive information. While allocentric orientation is mediated primarily by the hippocampus and its afferent and efferent connections, ESO is mediated by the prefronto-striatal system. Striatal lesions as well as classical neuroleptics, which block dopamine receptors, act through the prefronto-striatal

system and impair ESO. The purpose of the present study was to determine the effects of the atypical antipsychotics clozapine (0,5 mg/kg i.m.), olanzapine (0,5 mg/kg i.p.) and risperidone (0,5 mg/kg i.p.) which are believed to exert its antipsychotic effects mainly by dopaminergic, cholinergic and serotonergic mechanisms. A delayed-two-alternative-choice-task, under conditions that required ESO and at the same time excluded allocentric spatial orientation was used. Clozapine (and olanzapine) treated rats made more errors than risperidone treated rats in the delayed alternation in comparison with the controls. Motor abilities were not impaired by any of the drugs. Thus, with regard to the delayed alternation requiring ESO, clozapine and olanzapine but not risperidone affects the prefronto-striatal system in a similar way as classical neuroleptics do.

Keywords: allocentric spatial orientation, egocentric spatial orientation, motor abilities, dopamine receptors, classical neuroleptics, striatal lesions

Introduction.

Schizophrenia is an enigmatic illness that most often appears in the second or third decades of life, frequently leading to severe lifelong functional impairment if not treated adequately. Symptoms such as thought disorders, hallucinations and delusions are most dramatic and are labelled positive symptoms. Flattening of affect, poverty of speech, social withdrawal, deficits in working memory and deficits in other cognitive domains are called negative symptoms and may be the most functionally limiting (Crook and Hyde, 2001). The classical neuroleptic drugs used to treat schizophrenia are dopamine D2 receptor blockers, and reverse predominantly the positive symptoms. An unwanted side effect of these agents is the induction of motor symptoms resembling those of Parkinson's disease. These are labelled extrapyramidal motor symptoms (EPS) and can be acute or tardive.

Since they are very distressing for patients, much attention has been paid to those side effects of neuroleptic treatment.

Novel antipsychotics represent a significant advance in treatment of schizophrenia because of their reduced propensity to disrupt cognitive behavior and their lower risk of inducing motor side efects. The more benign side effect profile of the novel antipsychotics may be related to their shared serotonergic properties and it has been suggested that antagonism of the 5-HT2A receptors may mitigate the effects of D2 blockade thereby diminishing extrapiramidal side effects. (Rosengarten and Quartermain, 2002). Clozapine was the first of the novel group of atypical antipsychotic agents that lacks the EPS side effects but are effective in reducing the negative symptoms of schizophrenia, depressive symptoms and suicidal behaviour (Buchanan et al., 1998; Buckley, 1999). Clozapine interacts with higth or moderate afinity at serotonergic (5-HT2A, 5-HT2C and others) acetylcholinergic (muscarinic), adrenergic (α1, α2, β2), histaminic (H1) and other neurohumor receptors (Baldessarini and Frankenburg, 1991; Brunelo et al., 1995; Baldessarini and Tarazi, 1996) and also displays somewhat greater affinity for D4 receptors (Van Tol et al., 1991), suggesting that these receptors may represent potential sites of action of clozapine and perhaps other antipsychoticsagents.

Several newer atypical antipsychotics have emerged. Among them are the clozapine analogs olanzapine and the benzisoxazole derivative risperidone. Like clozapine, these compounds have multiple sites of molecular interaction and greater affinity for serotonergic 5-HT2A than DA D2 receptors (Bymaster et al., 1996; Schotte et al., 1996; Gunasekara and Spencer, 1998). This receptor-interaction pattern may contribute to low EPS risk (Meltzer et al., 1989).

In rats, classical neuroleptics induce a characteristic impairment in various maze tasks requiring egocentric spatial orientation (ESO) i.e. orientation according to internal representations. It is suggested that spatial information is organized into an egocentric cognitive map, similar to the models of O´Keefe and Nadel (1978) and Potegal (1982), based on memory for responses that depend upon accurate assessment of one´s body orientation in space, and an allocentric cognitive map

based on memory for specific stimuli representing places or relations between places that are independent of the body´s orientations in space. Furthermore, it has been proposed that medial prefrontal cortex in the rat mediates an egocentric cognitive map whereas the parietal cortex mediates an allocentric cognitive map (Kesner, Farnsworth, & DiMattia, 1989).

It is believed that dysfunction of the striatum underlies the egocentric localization deficit since rats with caudate lesions are deficient in ESO but perform normally in maze tasks requiring allocentric orientation (Cook and Kesner 1988).

The unique therapeutic efficacy of the atypical antipsychotics clozapine, olanzapine and risperidone led us to investigate whether or not ESO is also impaired by them. A delayed-two-alternative-choice-task (Y-maze) was applied, under conditions that required ESO and, at the same time, excluded allocentric spatial orientation.

Material and Methods

Subjects. For the clozapine experiment, sixteen male *Long-Evans* rats, weighting 200-300g, approximately 4 months old, were housed in groups of 8 per cage, under constant temperature (22-23°C) and humidity conditions (40-60%) in a 12h light : 12h dark cycle. Water was continuosly available and food (12 g of standard lab chow per animal per day) was provided in each day, after the experiment. Seven days prior to the beginning of each experiment, they were handled for about 10 minutes each day. For the olanzapine and risperidone experiments, thirty-two male albino Wistar rats, weighting 200-300g, approximately 4 months old, were housed in groups of 5 per cage, under constant temperature (22-23°C) and humidity conditions (40-60%) in a 12h light : 12h dark cycle. Water was continuosly available and food (12 g of standard lab chow per animal per day) was provided in each day, after the experiment.

Drug. Clozapine 50 mg (Novartis Pharma GmbH - Nüremberg, Germany) was diluted in neutral oil to reach the appropriate concentration (5,0 mg/kg). The appropriate drug dose or an equivalent volume of vehicle was administraded i.m. 60 min prior the start of the experiment each day. The clozapine group (n=8) was treated for 8 days with clozapine (0,5 mg/kg). The control group (n=8) was treated for 8 days with pure oil. The experiment was performed on 8 days for both groups. Olanzapine 10 mg (Eli Lilly, Indianapolis, USA) and risperidone (Biosintetica, SP, Brazil) were diluted in saline to reach the appropriate 0,5mg/kg concentration. The appropriate drug dose or an equivalent volume of vehicle was administraded i.p. 60 min prior the start of the experiment each day. Both groups (n=8) were treated with olanzapine and risperidone respectively for 8 days and the control group (n=8) was treated with saline. Like the clozapine experiment, the two experiments were performed on 8 days for both groups.

Behavioural Testing. A delayed two-alternative-choice-task was performed in a standard Y maze. On the first trial, rats were rewarded for traversing the runway and entering either arm. Thereafter, for a total of 10 trials per session, rats were rewarded only if they entered the maze arm which was not previously chosen, with the exception of the second run: in which the position of the pellet was alternated to the position of the pellet that has been eaten during the first run. The experiment was stopped, provided that either the pellet was eaten or a given time-limit was exceeded. Time-limit was 180 sec. At most, nine runs – concerning the delayed two-alternative-choice-task – were done by an individual subject per experimental day. The percentage of runs that include the wrong arm was defined as *relative error.* For the clozapine experiment, pellet consumption and runs were observed on a computer screen. For the another experiments (olanzapine and risperidone), the pellet consumption and the time were noted handy. In order to exclude conditions that allowed allocentric orientation, (eg. by

way of using visual patterns, light sources or olfactory gradients), orientation of the Y was changed every experimental day in a pseudo-randomized order.

Statistics. The performance of each group was analysed by the *Kruskal-Wallis One-Way Analysis of Variance* (ANOVA). To test for differences between the test and the control group, the *Wilcoxon Rank Sum/Mann-Witney U-Test* was used. Again, non-parametric tests were used for time-measurements because the cut-off time of 180 sec. The *Kruskal-Wallis One-Way Analysis of Variance* (ANOVA) was used for the measurement of error over time.

Results. Clozapine (0,5 mg/kg) impaired delayed response performance in the delayed-two-alternative-choice-task (Y-maze) (Fig 1). The effects of clozapine on locomotion were examined to determine whether clozapine induces motor impairment or not: in contrast to enhancement of errors, clozapine had no significant effects on locomotion in comparison with the vehicle control (Fig. 2). In some animals signs of sedation, but no catalepsy was observed (Fig. 2). The 0,5 mg/kg of olanzapine administraded also impaired the delayed response performance on the subjects in the Y-Maze (Fig 3). Differently of the clozapine, the running time of the olanzapine subjects was prolonged in comparison with the clozapine animals (Fig 4). A litlle catalepsy was observed at the dose of 0,5 mg/kg. On the other hand, the risperidone dose of 0,5 mg/kg impaired the delayed response performance only on the first four trials but had no effect during the later trials (Fig 5). In contrast, the running time of the risperidone subjects was also prolonged (Fig 6), like observed in olanzapine subjects (Fig 4), but not in the clozapine (Fig 2). No catalepsy or any motor impairments were observed in the treated subjects during this task.

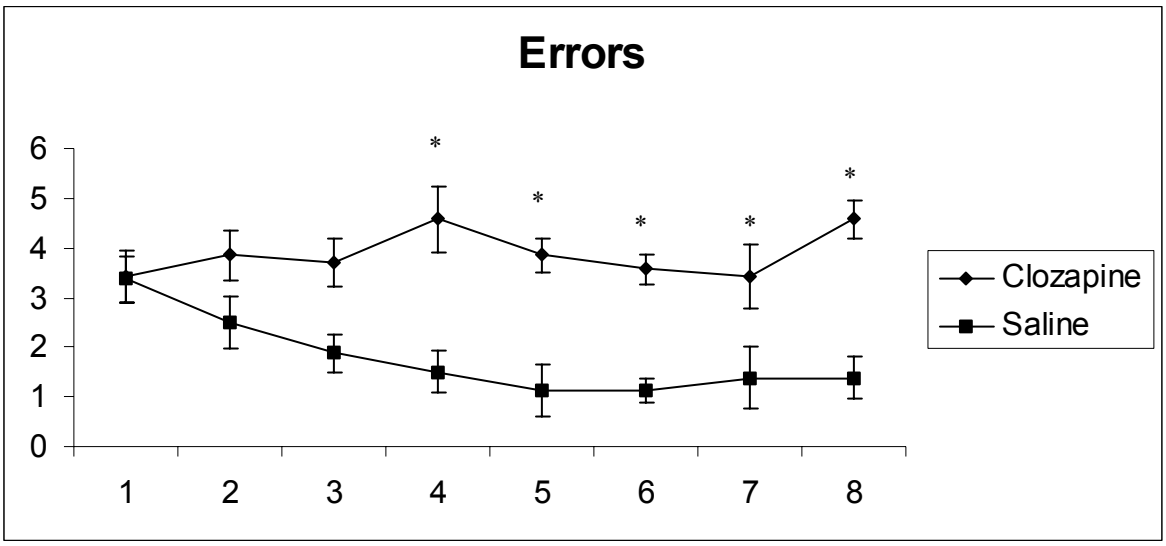

Fig. 1. Effect of daily clozapine (0,5 mg/kg i.m.) and saline (oil) treatment on a delayed two-alternative choice task in a Y-maze, under conditions that required egocentric spatial orientation. Rats had to perform up to 9 runs per experimental day, with breaks in between one hour after drug treatment. A run into a not rewarded arm was counted as an error ($p < 0,05$ in *t-test*)

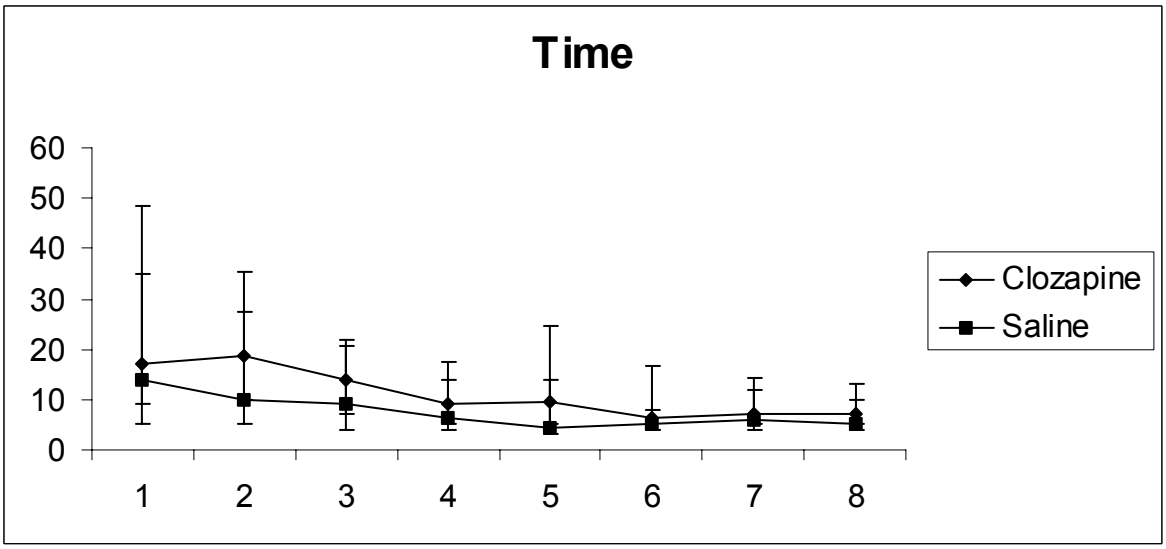

Fig. 2. Effect of clozapine (0,5mg/kg i.m.) plus saline (oil) treatment on a delayed two-alternative choice task in a Y-maze, under conditions that required egocentric spatial orientation. Rats had to perform up to 9 runs per experimental day, with breaks in between one hour after drug treatment. For running time, time up to consumpion of the pellet was measured ($p < 0,05$ in *Mann-Witney U-Test)*

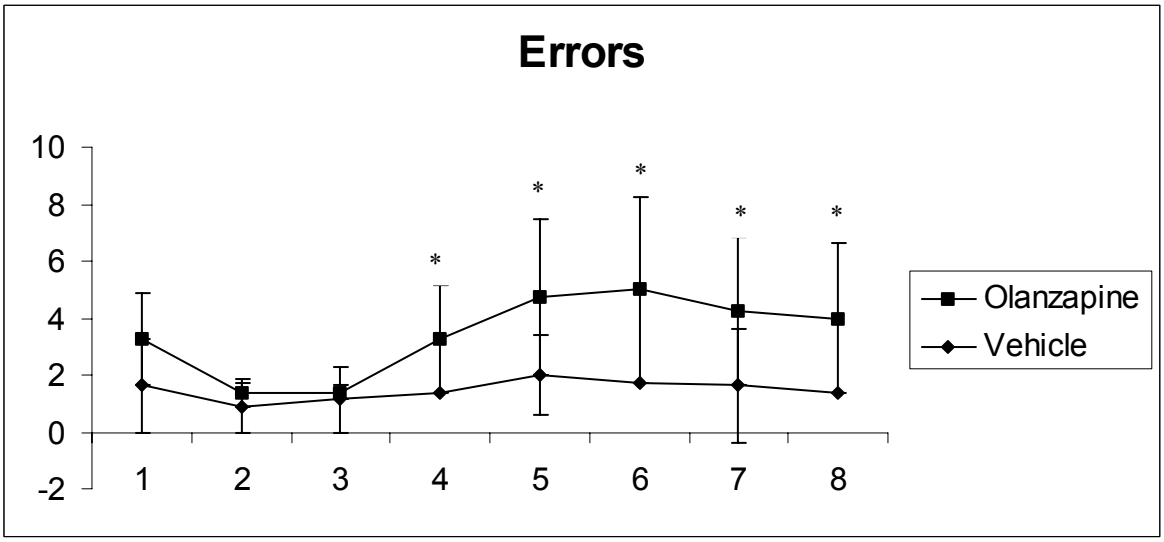

Fig. 3. Effect of daily olanzapine (0,5 mg/kg i.p.) and saline treatment on a delayed two-alternative choice task in a Y-maze, under conditions that required egocentric spatial orientation. Rats had to perform up to 9 runs per experimental day, with breaks in between one hour after drug treatment. A run into a not rewarded arm was counted as an error ($p < 0,05$ in *t-test*).

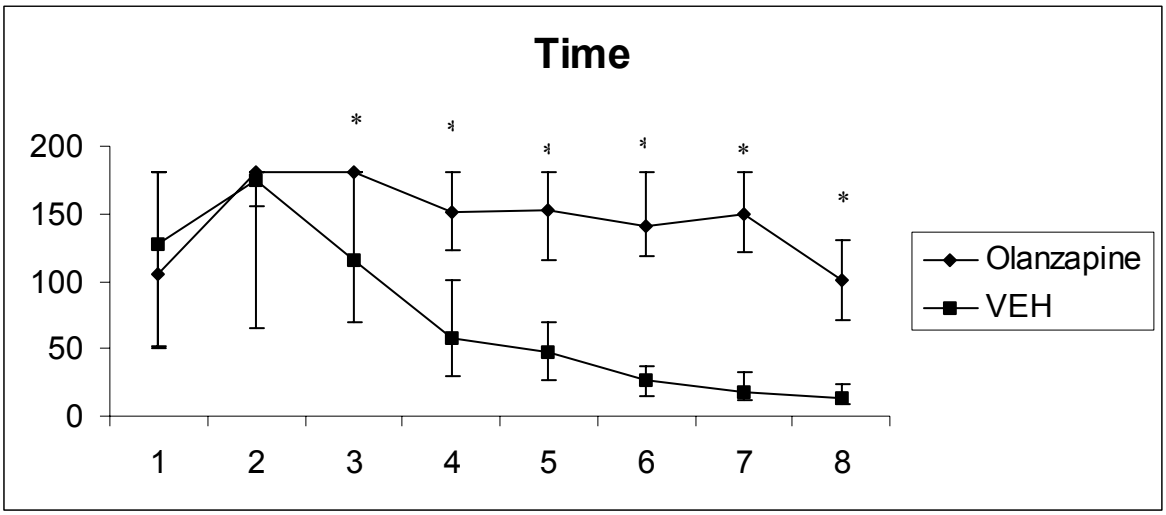

Fig. 4. Effect of olanzapine (0,5mg/kg i.p.) and saline treatment on a delayed two-alternative choice task in a Y-maze, under conditions that required egocentric spatial orientation. Rats had to perform up to 9 runs per experimental day, with breaks in between one hour after drug treatment. For running time, time up to consumpion of the pellet was measured ($p < 0,05$ in *Mann-Witney U-Test)*

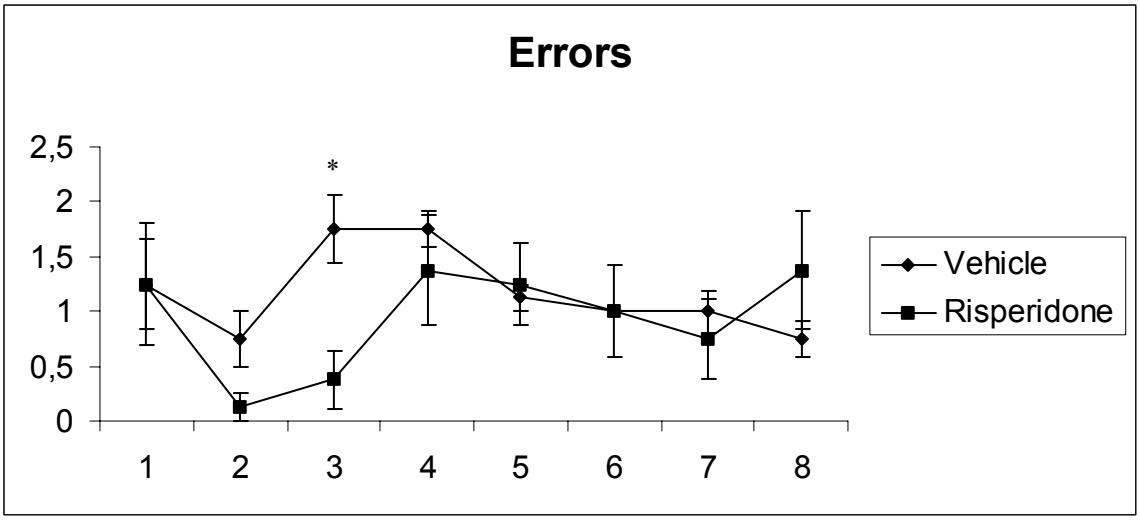

Fig. 5. Effect of daily risperidone (0,5 mg/kg i.p.) and saline treatment on a delayed two-alternative choice task in a Y-maze, under conditions that required egocentric spatial orientation. Rats had to perform up to 9 runs per experimental day, with breaks in between one hour after drug treatment. A run into a not rewarded arm was counted as an error ($p < 0,05$ in *t-test*).

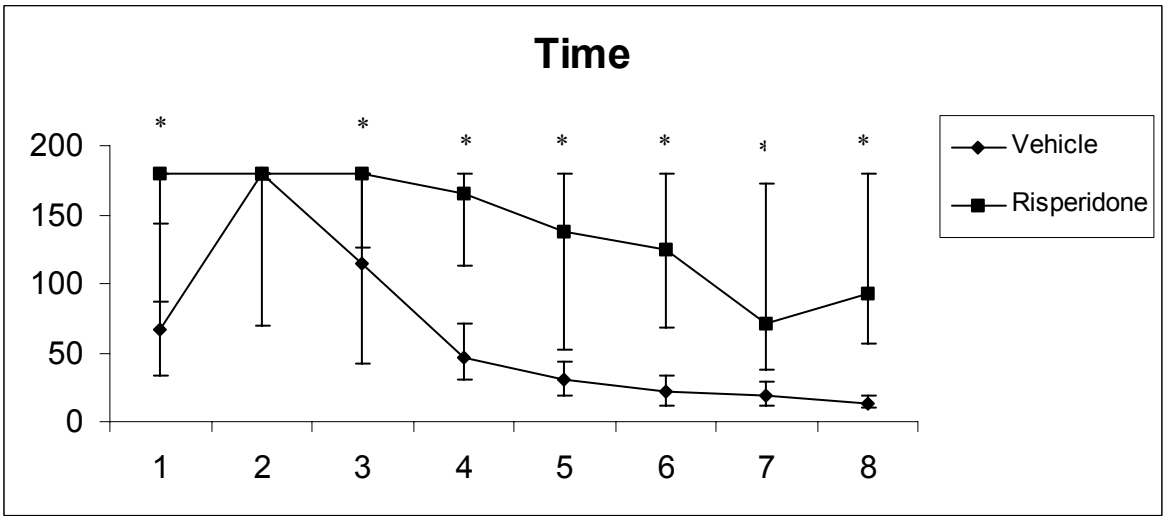

Fig. 6. Effect of risperidone (0,5mg/kg i.p.) and saline treatment on a delayed two-alternative choice task in a Y-maze, under conditions that required egocentric spatial orientation. Rats had to perform up to 9 runs per experimental day, with breaks in between one hour after drug treatment. For running time, time up to consumpion of the pellet was measured ($p < 0,05$ in *Mann-Witney U-Test)*.

Discussion. The main finding of this study was that clozapine, olanzapine but not risperidone disrupted the performance of the Y-maze task, suggesting that some but not all, types of atypical antipsychotics drugs disturb egocentric spatial orientation in rats. Motor coordination was not disrupted by any drugs of this experiment.

The reasons for differences among novel atypical antipsychotics in liabiliity to disrupt cognitive function remains unclear (Rosengarten and Quartermain, 2002). Its well known that dopamine D2 receptor blockade impairs spatial learning and memory (Skarsfeldt, 1996) and this may be a partial explanation for the effects of clozapine and olanzapine in the present study but it is unlikely to the risperidone effects, that caused less overall disruption of spatial performance. In the case of clozapine, which has relatively low D2 receptor occupancy but has relatively higther affinity for cholinergic receptors than olanzapine (Zhang and Bymaster, 1999), the disruptive effects may result from combination of modest D2 receptor

occupancy and antagonism of cholinergic receptors. Risperidone has a hight ratio of serotonin 5-HT_2 receptor binding to D2 binding (Schotte et al., 1996; Kapur et al., 1997; Knable et al., 1997; Zhang and Bymaster, 1999) and may have different effect on cognitive function than other antipsychotics. It has been suggested that hight 5-HT_{2A}-to-D2 ratio may reduce the occurence of dyskinesia (Kapur et al., 2000) . This findings could be a partial explanation for the no disruptive effects that was observed in the administration of risperidone in the present study. In addition, risperidone has moderately higth affinty for D2 receptors and a very low affinity for dopamine D1 receptors (Zhang and Bymaster, 1999). The dose of risperidone used in our study was relatively low. This probably resulted in a relatively low rate of spatial impairment during the task. Risperidone, which has a hight D2 receptor occupancy, also has a higth affinity for 5-HT_2 receptors (Knable et al., 1997; Schotte et al., 1996; Zhang and Bysmaster, 1999) and it has been suggested that this may act to counterbalance the D2

stimulation, thereby reducing the occurence of spatial orientation impairments.

Our results fit with those published of Kesner (1986) and Kesner and DiMattia (1987) who have proposed that the striatum plays a critical role in memory for egocentric responses that is based on proprioceptive and vestibular feedback mechanisms (Adams, Kesner & Ragozzino, 2001; Cook & Kesner, 1988; Duncan-Davis, Filoteo & Kesner, 1996; Ghiselli & Brown, 1938; Kesner, 1998; Kesner et al., 1993; Potegal, 1969). Furthermore, there are studies that support the hypothesis that the striatum plays a significant role in structural organization of memory by encoding spatial response attributes. For example, rats with caudate lesions are deficient in learning a maze require alternative right-left runs, but perform like controls in learning a maze task not requiring right-left alternations (Borst, Delacour, & Libauban, 1970). The effect of clozapine and the olanzapine in choosing the right-left arm indicate that blockade dopaminergic pathways in the striatum may impair performance in a

delayed-two-alternative-choice-task by increasing regressive errors, what is a clue that the dopaminergic pathway plays a important role in mediating egocentric localization. These results suggest that the striatum and limbic areas may influence distinct processes that enable motor movements and behavioural flexibility (Ragozzino, Kesner & Mizumori, 2002). In support of this idea, findings from some studies indicate that striatal lesions in rats impair short-term memory for a particular motor response, that is, remembering whether a left or right turn was just made, as well as retention of a learned response pattern (Colombo, Davis, & Volpe, 1989; Cook & Kesner, 1988, Kesner et al., 1993; Potegal, 1969). Results from other investigations suggest that the deficit arises not from an inability to remember a particular response, but rather an impairment in forming the appropriate stimulus-response association (Aosaki, Kimura, & Graybiel, 1995; Colombo et al., 1989; McDonald & White, 1993, 1994; Mishkin, Malamut & Bachevalier, 1984; Packard, 1990; Packard et al., 1989; Packard &

McGaugh, 1996; Winocur & Eskes, 1998). The pattern of increased errors observed following striatal dysfunction is analogous to findings in Parkinson´s disease (Downes et al., 1989; Flowers & Roberston, 1985).

The prefrontal cortex is specifically involved in working memory and thus for execution of delayed alternation behaviour. Additionally the prefrontal cortex works in close connection with the striatum. Since there are sound hints, that clozapine and olanzapine affects also the prefrontal cortex, it is possible that the effects of this drugs on ESO are mediated by the prefrontal cortex (Owen et al., 1993; Wise, Murray, & Gerfen, 1996). Assuming that clozapine and olanzapine inactivates prefrontal functions, rats may continue to use the previously reinforced response pattern, either because it is not being suppressed or because new response options have not been generated (Ragozzino, Kesner & Mizumori, 2002).

In conclusion, the present experiments demonstrate that novel atypical antipsychotics are a heterogenous group of drugs differing in pharmacological profile and locus of action in the brain. Much remains to be learned about their side effect especialy on cognitive behaviors and spatial orientation. It is becoming apparent that some novel atypical antipsychotics can have significant disruptive effects on cognitive behaviors, especially on learning and memory.

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DISCUSSÃO

Os resultados do presente trabalho sugerem que os efeitos dos antipsicóticos atípicos clozapina e olanzapina, mas não risperidona, prejudicam a OEE em ratos. A administração de doses relativamente baixas das três drogas não causou nenhum efeito motor prejudicial em ambas as tarefas. Os resultados sugerem que os antipsicóticos atípicos clozapina, olanzapina e risperidona, com relativamente baixa afinidade por receptores dopaminérgicos D2 (Haleem et. Al., 2002) não prejudicam a coordenação motora.

É sabido que o bloqueio de receptores dopaminérgicos D2 prejudica o aprendizado espacial e a memória (Skarsfeldt, 1996). Isso poderia ser uma explicação parcial para os efeitos observados tanto com a administração de clozapina como de olanzapina em relação aos erros cometidos na alternância de escolhas que a tarefa estudada exige, mas não com relação a risperidona, que não prejudicou o desempenho espacial em relação aos animais controle. Os efeitos da clozapina poderiam ser atribuídos a sua possível ligação aos receptores dopaminérgicos D2 conjuntamente com o alto antagonismo colinérgico, já que é sabido que esta droga possui baixa afinidade por receptores D2, mas relativamente alta afinidade por receptores colinérgicos em relação a olanzapina (Tarazi et al., 2001).

A risperidona tem um alto grau de afinidade por receptores 5-HT2 vinculados sinapticamente a receptores dopaminérgicos D2 (Schotte et al., 1996; Kapur et al., 1997; Knable et al., 1997; Zhang and Bymaster, 1999) e pode atuar

farmacologicamente de uma forma diferente aos outros antipsicóticos. Tem sido sugerido que a interação dos receptores 5-HT_{2A}-para-D2 pode reduzir a ocorrência de disquinésia (Kapur et al., 2000). Isto poderia ser uma explicação parcial para os efeitos não deletérios da risperidona neste estudo. Adicionalmente, a risperidona tem uma alta afinidade por receptores D2 e uma baixa afinidade por receptores D1 e a dose utilizada nesse estudo foi relativamente baixa.

Kesner (1986) e Kesner e DiMattia (1987) propuseram que o striatum tem um papel importante na memória para respostas egocêntricas e estas estão baseados em mecanismos proprioceptivos (Adams, Kesner & Ragozzino, 2001; Cook & Kesner, 1988; Duncan-Davis, Filoteo & Kesner, 1996; Ghiselli & Brown, 1938; Kesner, 1998; Kesner et al., 1993; Potegal, 1969). Além disso, existem estudos que apoiam a hipótese que o striatum participa significativamente no que se diz respeito à organização estrutural da memória em estruturar atributos de respostas espaciais. Por exemplo, ratos com lesões no núcleo caudato são deficientes em aprender uma tarefa que requer alternância de escolhas (como no labirinto em Y) mas percorrem como animais controle em um maze que não requer alternâncias de escolhas (Borst, Delacour, & Libauban, 1970). O efeito de clozapina e olanzapina em escolher o braço correto na alternância de escolhas indica que vias dopaminérgicas bloqueadas no striatum podem prejudicar a performance na tarefa aqui estudada por aumentarem os erros de escolha no decorrer do experimento. Isto sugere que a via dopaminérgica possa ter um papel importante na mediação da orientação espacial (White et al., 1993; White and Viaud, 1991). Estes resultados também sugerem que o striatum e áreas límbicas podem influenciar processos distintos que habilitam movimentos motores e a flexibilidade comportamental (Ragozzino, Kesner & Mizumori, 2002). Sustentando essa idéia, achados de outros estudos indicam que lesões estriatais prejudicam a memória de curta duração ou short-term memory para uma resposta motora particular, ou seja, lembrar quando uma alternância de braço foi recentemente feita assim como

a retenção do mesmo modelo aprendizado (Colombo, Davis, & Volpe, 1989; Cook & Kesner, 1988, Kesner et al., 1993; Potegal, 1969). Resultados de outras investigações indicam que os déficits surgem não da habilidade em não aprender uma resposta particular, mas sim em um enfraquecimento ou dano na formação da associação do estímulo-resposta apropriado (Aosaki, Kimura, & Graybiel, 1995; Colombo et al., 1989; McDonald & White, 1993, 1994; Mishkin, Malamut & Bachevalier, 1984; Packard, 1990; Packard et al., 1989; Packard & McGaugh, 1996; Winocur & Eskes, 1998).

O cortex pré-frontal é envolvido na formação da memória de trabalho, necessária para a execução de tarefas que exigem alternância de escolhas. Adicionalmente, o córtex pré-frontal trabalha em íntima conecção com o striatum. (Ragozzino, Kesner and Mizumori, 2002) Assim, seria possível sugerir que a administração das drogas clozapina e olanzapina afetaram o córtex pré-frontal e que seus efeitos na OEE podem ser mediados pelo córtex pré-frontal (Owen et al., 1993; Wise, Murray, & Gerfen, 1996). Assumindo que tanto a clozapina quanto a olanzapina inativaram a função cortical pré-frontal, os ratos podem utilizar o mesmo modelo de escolha previamente escolhido (Ragozzino, Kesner & Mizumori, 2002).

Em conclusão, o presente estudo demonstra que os novos antipsicóticos atípicos clozapina, olanzapina e risperidona, na dose de 0,5 mg/kg podem ter efeitos negativos sobre funções cognitivas dependentes da OEE.

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