Active allothetic place avoidance task in study of cognitive disturbance in animal model of schizophrenia in rats

Lukas Rambousek[1,2], Karel Vales[1], Jana Kenney[1], and Ales Stuchlik[1]
[1]*Department of Neurophysiology of Memory and Computational Neuroscience, Institute of Physiology, Academy of Sciences, Prague, Czech Republic, rambosuek@biomed.cas.cz*
[2]*Department of Organic Technology, Institute of Chemical Technology Prague, Czech Republic*

Since the ethiopathology of schizophrenia is not fully understood, it is difficult to establish its animal model with full construct validity. Recently applied models are based on the central blockade of glutamate receptors, namely their NMDA subtype. It has been observed that administration of compounds that block NMDA receptor-dependent neurotransmission (phencyclidine, ketamine, dizocilpine) elicits a psychotic state when applied to healthy humans and worsens the psychotic symptoms when administered to schizophrenic patients [1]. Application of high-affinity non-competitive NMDA-receptor antagonist MK-801 (dizocilpine) was proposed as an animal model of schizophrenia which proved to have relatively high predictive validity [2]. Animals treated with MK-801 exhibit typical changes in behavior including hyperactivity, stereotypic behaviors, defective habituation, impaired attention, simpler behavioral repertoire and general behavioral primitivization [3].

Testing the cognitive abilities of animals with experimentally induced psychotomimetic state requires specific behavioral paradigms, which should be dry land-based (more natural than the Morris water maze) and, what is more important, they should have a relatively high cognitive demand for their efficient solution [4]. Morris water maze or radial maze focus on testing allocentric memory processes and they do not sufficiently cover other cognitive functions. By contrast, the Active Allothetic Place Avoidance test (AAPA) is useful for detecting cognitive disorganization. We propose that AAPA requires more complex cognitive abilities than classical behavioral paradigms. The principle of function of the place avoidance tasks is that rats are moving on a uniform circular arena, on which an arbitrarily located unmarked sector is defined, entering of which is punished by a mild footshock.

Briefly, AAPA setup consists of a smooth metallic circular arena (80 cm in diameter) enclosed with a 30 cm high transparent Plexiglas wall and elevated 1m above the floor of the experimental room containing many visual landmarks. At the beginning of each training session, a rat was placed on the rotating arena (1 rpm), where a directly imperceptible 60◦ to-be-avoided sector (shock sector) was defined by the custom-based computerized tracking system, located in an adjacent room. The location of the shock sector could be determined exclusively by its spatial relations to distal orienting cues located in the room. The rat wore an infrared light-emitting diode (LED) fixed between its shoulders with a light latex harness, and its position was tracked every 40 ms and recorded onto a computer track file, allowing subsequent reconstruction of the track with an off-line analysis program (TrackAnalysis, Biosignal Group, USA). Whenever a rat entered the shock sector for more than 0.5 s, mild electric shocks (50 Hz, 0.5 s) were delivered in intervals of 1.5 s until the rat left the shock sector for at least 0.5 s. The shocks were delivered through a thin subcutaneous low-impedance wire implant on the back of the rat standing on the grounded floor. The appropriate shock current (ranging between 0.2 and 0.7 mA) was individualized for each rat to elicit a rapid escape reaction but to prevent freezing. Since, the arena was rotating; the rat had to move actively away from the shock in the direction opposite to the arena rotation, otherwise it was passively transported to the shock sector. Experimental sessions in AAPA lasted 20 min and each rat had one session every day, carried out during daylight hours.

Successful performance of the task requires that the animal identifies its position in the room frame and also the position of the shock sector in the room frame. Since the arena-frame information (droppings, urine and scent marks self-generated by rats) rotates with respect to the shock sector the animal must also recognize these arena-based cues as distinct from the stimuli that come from the room frame and ignore the irrelevant arena-frame for localization of the shock sector. Such an ability was described to be hippocampus-dependent and called "cognitive coordination". This requirement that the subject differentiates between relevant and irrelevant stimuli is similar to the concept that schizophrenic patients are often unable to differentiate between relevant and irrelevant stimuli because their information processing is impaired.

This research was supported by grants IGA-MH-NR/9178-3, GACR-309/07/0341, and MEYS-CR-project-1M0517.

References

1. Coyle JT, Tsai G, Goff D. (2004). Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. *Ann. NY Acad. Sci.,* **1003**, 318-327.
2. Farber N.B. (2003). The NMDA-receptor hypofunction model of psychosis, *Ann. N.Y. Acad. Sci.*, **1003**, 119–130.
3. Koek W, Woods JH, Winger GD. (1988) MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. *J. Pharmacol. Exp. Ther.*, **245**, 969-974.
4. Stuchlik A., Rezacova L, Vales K, Bubenikova V, Kubik S. (2004). Application of a novel Active Allothetic Place Avoidance task (AAPA) in testing a pharmacological model of psychosis in rats: comparison with the Morris Water Maze. *Neurosci. Letters*, **366**, 162-166.