P.1.d.007 Different sensitivity to dihydrexidine in the delayed matching and non-matching to position tasks

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Working memory (WM) is often conceptualised as the utilization of information over short intervals; typically associated with prefrontal cortical activity in rats and humans. WM can be categorised as transient (e.g. holding and repeating a series of numbers such as a telephone number) or executive function which involves additional processing of the transient information (e.g. the digit span backwards task). Both delayed matching to position (DMTP) and delayed non-matching to position (DNMTP) tasks are considered to tax working memory and have be shown to also depend upon prefrontal cortex function (Sloan et al., 2006). In this study we investigated the effects of the dopamine D1 agonist dihydrexidine in the DMTP and DNMTP tasks in unimpaired rats. This compound has previously been shown to improve cognitive performance in impaired rats and in MPTP treated monkeys as well as increasing cFOS activation in the prefrontal cortex.

Unimpaired male Lister Hooded rats were trained on either the DMTP or DNMTP tasks. Animals were required to respond on a lever when presented with a a lever and the light stimulus above it. A delay period of between 1 and 32 seconds then began. At the end of the delay, a head entry into the recessed magazine initiated the choice phase. Rats were then required to match (DMTP), i.e. press the same lever, or, not match (DNMTP), i.e. press a different lever, to the sample lever to earn a food pellet and a 5 s inter-trial interval (ITI) began. If animals failed to make the appropriate responses, the trial was recorded as an omission, the house-light was switched off, and the ITI proceeded in darkness. Dihydrexidine (0.25–5 mg/kg) in DMTP or (1–5 mg/kg) in DNMTP was given sub-cutaneously in 5% glucose, 30 minutes before the start of the session.

Dihydrexidine produced dose-related delay-dependant deficits in the DMTP task. Significant effects were seen at 1 mg/kg on % correct responding; more robust effects were seen at 2.5 and 5 mg/kg on % correct responding, % omissions and number of head entries. In addition there were also significant effects on session length, latency to make a response and index Y (a measure of response bias). However, in the DNMTP task the only affected measures were head entries, session length and average latency to make a response and these effects were only seen at 5 mg/kg suggesting that the effects were motoric rather than mnemonic in this task.

A bell-shaped curve has been postulated for the relationship between working memory performance and D1 signaling (Williams and Goldman-Rakic 1995). Behavioral studies have confirmed that excessive D1 signaling in PFC is deleterious to cognition (e.g. Arnsten 2000). As demonstrated by these studies, D1 agonism does not improve cognition in normal and highly trained animals, possibly relating to the inverted U-shaped concentration required for optimal performance. However, these data show that DMTP and DNMTP assays are differentially sensitive to D1 agonism and may not recruit or utilize the same neuronal or pharmacological substrates.

References

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P.1.d.008 Effects on the adult behavioral changes of early maternal separation during the stage of development in the rat

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Objectives: The exact cause of abnormal behavior in a variety of mental disorders including schizophrenia and depression has largely unknown. There is increasing evidence that genetic and early enviromental factors interact to disturb the normal development of the brain. Maternal separation in animal during the early stage of development has been shown to alter adult behavior and neurochemical function. Nitric oxide (NO) has recently been discovered to be an important intracellular and intercellular messenger in the brain glutamatergic N-methyl-D-aspartate (NMDA) pathway. NO might have been known to play a crucial role in the neurodevelopment. Many evidences have been shown that the glutamatergic NMDA-NO system may be involved in the developmental pathophysiology of a variety of mental disorders. This study was designed to elucidate the adult behavioral effect of early maternal separation during the stage of development in the rats. The study was also aimed to investigate the involvement of glutamatergic NMDA-NO system in the adult behavioral changes of early maternal separation during the stage of development. Methods: Pregnant female Sprague-Dawley rats were observed for delivery (postnatal day 0). Subjects which were derived from the litters were divided into two groups. Experimental group ($n = 24$) consisted of subjects which were removed and weaned from the dams on postnatal day 15. Control group ($n = 24$) were the litters that experienced no maternal separation until postnatal day 21. On postnatal day 35 baseline locomotor activity was recorded in polycarbonate box ($50 \times 50 \times 50$ cm) for 30 minutes using computerized automatic analysis program (Neurovision Analysis by Pusan National University, Korea). And then, the experimental group and control group were randomizedly divided into three subgroups, respectively. Three subgroups in each group were injected NMDA receptor antagonist MK-801 (0.5 mg/kg), nitric oxide synthase inhibitor Nω-nitro-L-arginine (L-NA, 20 mg/kg), and vehicle, respectively. Ten minutes later, locomotor activity was measured again the same way.

Results: Locomotor activity was significantly diminished in maternal separation group compared to control group ($p < 0.001$). After treatment with MK-801, locomotor activity was significantly increased both in maternal separation group ($p < 0.001$) and in control group ($p < 0.05$). The increase of locomotor activity was much greater in maternal separation group than in control group ($p < 0.001$). After treatment with L-NA, locomotor activity was also significantly increased in maternal separation group. There was, however, no difference of locomotor activity in control group between before and after treatment with L-NA.

Conclusions: These results certify that maternal separation during the early stage of development in the rats can lead to behavioral abnormalities in adulthood. The neurochemical mechanism of adult behavioral effect of maternal separation may be related to the glutamatergic NMDA – NO system. It is indirectly