Physiology & Behavior 173 (2017) 243–251

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

The effects of low dose MK-801 administration on $NMDA_R$ dependent executive functions in pigeons

Nurper Gökhan [a], Lorenz S. Neuwirth [b,c], Edward F. Meehan [d,e,*]

[a] LaGuardia Community College, (CUNY) Department of Social Sciences, Long Island City, NY 11101, United States
[b] SUNY Old Westbury, Psychology Department, Old Westbury, NY 11568, United States
[c] SUNY Neuroscience Research Institute, Old Westbury, NY 11568, United States
[d] The College of Staten Island (CUNY), Psychology Department, Staten Island, NY 10314, United States
[e] The Center for Developmental Neuroscience, Staten Island, NY 10314, United States

HIGHLIGHTS

- Effects of low dose MK-801 on fronto-executive function were studied in avians.
- Excitatory and inhibitory performance was disrupted by MK-801.
- MK-801 did not affect previously learned task in a cross-over.
- Inhibition returned quickly, but excitation failed to fully recover over 3 months.
- Avians serve as translational models for neurocognitive research.

ARTICLE INFO

Article history:
Received 4 October 2016
Received in revised form 8 February 2017
Accepted 8 February 2017
Available online 10 February 2017

Keywords:
Executive function
$NMDA_R$
MK-801
Avian model
Schizophrenia
RDoC

ABSTRACT

An avian analogue of human fronto-executive dysfunction was used to study the long-term effects of a repeated low dose of MK-801. MK-801 is known to selectively antagonize the excitatory *N-methyl-D-aspartate receptors* ($NMDA_R$) and indirectly impair inhibitory related processes ($GABA\text{-}_{AR}$). First, eight pigeons were divided into two groups, receiving either 0.15 mg/kg MK-801 or saline (i.p.) 1-hour prior to each session. Thirty 90-min sessions of a Differential Reinforcement of Low Rate of Response (DRL-10s) schedule were run over 3-months. Both overall number of responses and efficiency were unaffected by treatment, establishing a sub-threshold motoric dose. Then, another eight pigeons, treated identically, were given an operant visual discrimination task. Results demonstrated impairment of the fronto-striatal function of both excitatory and inhibitory processes in the MK-801 group during the entire 3-months. A 30-session treatment cross-over showed that the Saline-to-MK-801 group was unaffected, whereas the MK-801-to-Saline group exhibited rapid recovery of inhibitory control, however excitatory control did not fully recover. Together, these results suggested that the $NMDA_R$ system is involved in the acquisition of excitatory learning, but only in the expression of inhibitory learning. Our findings were discussed in terms of the value of avian models in translational research. Furthermore, our results were examined within the context of the NIH Research Domain of Criteria initiative and the role of $NMDA_R$ disruption, which underlie executive dysfunction in various neuropsychiatric disorders. Finally, our findings suggested that the potential long-term effects of the clinical and recreational use of $NMDA_R$ antagonists require further study.

1. Introduction

Antagonism to *N-methyl-D-aspartate receptors* ($NMDA_R$) in animal models of learning and memory have been extensively used to investigate human neurocognitive impairments, assaying the molecular underpinnings of fronto-executive dysfunction consistent with disorders such as schizophrenia [1–4]. In addition, subtler forms of fronto-executive dysfunction have been investigated in well-designed procedures incorporating simple 2-choice discrimination tasks, match-to-sample learning, and cognitive-set shifting using rodents [5–7]. Fronto-executive dysfunction emanates from the disruption of the excitation dependent Glutamatergic $NMDA_R$ systems [3]. Studies have reported that low doses of $NMDA_R$ antagonists interfere with executive control of the ongoing and adaptive motivated behavior in animals. As such, low dose $NMDA_R$ antagonism interrupts sensori-motor control necessary for ongoing behavioral adaptations by a loss of or reduced

* Corresponding author at: The College of Staten Island of The City University of New York, 2800 Victory Boulevard, 4S-101, Staten Island, NY 10314, United States.
E-mail address: edward.meehan@csi.cuny.edu (E.F. Meehan).

http://dx.doi.org/10.1016/j.physbeh.2017.02.009
0031-9384/

ability to engage in cognitive shifts and may contribute to the negative symptoms associated with schizophrenia [4]. Therefore, low dose $NMDA_R$ antagonism can negatively impact learning through the desynchronization of sensori-motor and attentional processes, and further reduces motivation. In contrast, high dose $NMDA_R$ antagonism or brain lesion(s) results in Glutamatergic hypo-activity *via* the suppression of glutamate receptors, that in turn, aberrantly increases and desynchronizes fronto-executive dopamine signaling most associated with the positive symptoms of schizophrenia [8]. Thus, both low and high dose $NMDA_R$ antagonism are invaluable to elucidate the specific mechanisms that regulate fronto-executive function. However, the majority of research has focused solely on Glutamatergic excitatory-dependent processes, and has lacked the assessment of GABAergic inhibitory-dependent learning that is inversely affected by $NMDA_R$ antagonism. For example, $GABA\text{-}_{AR}$ antagonism by picrotoxin has been reported to reduce prepulse inhibition at the behavioral level, and GABAergic tone in the medial prefrontal cortex, disrupt prefrontal cortical sensorimotor gating over excitatory behavioral and executive control at the cellular and physiological levels [9]. Thus, the neuropsychology of executive dysfunction cannot be fully understood without an equal assessment of both excitatory- and inhibitory-dependent control of behavior.

Neuropathological considerations of systems involved in disrupting the balance of the $NMDA_R/GABA\text{-}_{AR}$ have been increasingly popular areas of investigation and overlap with the U.S National Institute of Health (NIH) Research Domain of Criteria (RDoC) initiative [10,11] targeting the foundations for clinical disorders. For example, animal models of schizophrenia based on $NMDA_R$ antagonism primarily evolved from psycho-motoric symptoms observed in *phencyclidine* (PCP) sensitized rats as a face valid model that compared directly to individuals with schizophrenia [12]. However, despite these similarities, PCP-induced psychosis in humans produces a limited subset of symptoms, but not the gradual cognitive and motivational decline seen in schizophrenia. Since rodents may not encode information through their visual sensorimotor systems as humans, the external validity of this model is questionable. In contrast to the rodent models of fronto-executive processes, avian models present an attractive alternative. Birds have a superior executive visual system and further have evolved with parallel cognitive features consistent with human higher order executive control systems [13,14]. Our understanding of the human CNS has recently benefited from the investigation of the evolution of avian brain structures and function [15–17]. In addition, the use of pigeons in learning and memory studies as an invaluable model across various tasks is well-established [18,19]. The longstanding operant procedures (*i.e.*, Instrumental conditioning) employed with avians are sensitive and reliable to gauge neurobehavioral executive functioning in real time (*i.e.*, continuous performance), which are modulated in avians through the *Nidopallium Caudolaterle* (NCL) network [6,20]. Early research confirmed that the $NMDA_R$ rich human prefrontal cortex (PFC), basal ganglia (BG) circuitry, along with the nucleus accumbens were critical for acquiring the executive regulation of motivated responding through Pavlovian conditioning under instrumental context-dependent control [21]. Thus, the fronto-striatal pathway, which is the NCL in avians, is fundamentally responsible for synchronizing the involvement of sensori-motor and attentional $NMDA_R$ circuits associated with Stimulus-Response-Outcome (S-R-O) relationships. As a model, S-R-O relationships account for networks that span across higher order neurocognitive centers, thus identifying $NMDA_R$ activity as the functional intersection of Pavlovian and Instrumental conditioning [22–24]. Therefore, avian research using operant procedures may be an ideal translational model in revealing the relative contribution of excitation and inhibition in executive control.

There are irrefutable neurocognitive deficits attributed to the three main $NMDA_R$ antagonists (*i.e.*, PCP, ketamine, and MK-801) [25–28]. Notably, low doses of MK-801 and ketamine both appear to negatively affect $NMDA_R$-dependent learning specifically during the acquisition phase of fronto-executive based tasks without inducing sensorimotoric distortion [1,2,29,30]. Additionally, research indicates that MK-801 may have a higher binding affinity for the Glutamatergic $NMDA_R$, and as a result further modulates cognition indirectly through both the dopamine transporter and D_{2R} [25–28]. However, most of these studies examined the role of $NMDA_R$ antagonists primarily in the initial acquisition phase and did not consider their effects on the long-term performance of a learned discrimination. Therefore, the intention of our present study was to examine the potential effects of long-term (3-months) use of MK-801. In addition, given the lack of research on the concurrent role of excitatory and inhibitory stimulus control within the same experimental context [29,30], our study was designed to tease apart the relative contribution of the $NMDA_R$ system in acquisition of behavior under simultaneous excitatory- and inhibitory-dependent control. The present study used a discrimination-generalization operant procedure sensitive enough to show the effects of $NMDA_R$ antagonism on both excitatory and inhibitory fronto-executive processes.

In strong doses, both ketamine (6 mg/kg i.p.) and MK-801 (0.5 mg/kg i.p.) induce hyperactivity before a complete motoric collapse [7], which obscures the ability to examine their effects on fronto-executive function. *Experiment 1* was conducted to confirm whether 0.15 mg/kg of MK-801 was an appropriate sub-threshold dose by presenting an executive task that required motor control. We used the traditional Differential Reinforcement of Low Rate of Response schedule (DRL-10s), which requires the pigeon to withhold its responses for an Inter-Response-Time of 10 s or more for the response to be rewarded. *Experiment 2* was conducted to assess fronto-executive functioning by gauging the stimulus control of responding to one stimulus (S+) that signaled rewards were intermittently available and another stimulus (S−) during which responding was never reinforced. This discrimination procedure thereby, mirrored a behavioral task wherein both excitation to S+ must be acquired and maintained while withholding responses to S− *via* inhibitory control. Our study aimed to clarify whether $NMDA_R$ antagonism under MK-801 results from a direct disruption of Glutamatergic excitatory-dependent neuronal activity or indirectly from the influence of GABAergic inhibitory-dependent processes as well. Furthermore, a cross-over design was used to determine whether any disruptive effects were permanent. Finally, we speculated that our experimental design would elucidate the link between $NMDA_R$ antagonism and fronto-executive dysfunction in relation to the $NMDA_R$ regulated networks that have been implicated in many neuropsychiatric disorders.

2. Method

2.1. Subjects

Sixteen experimentally naive White Carneaux pigeons (*Columba livia*) of mixed gender, aged ($M = 6.75$ years, $SD = 0.83$) from the Palmetto Pigeon Plant (Sumter, SC) were maintained at 80% of their *ad-libitum* weight. All subjects were randomly assigned to both treatment and experimental conditions. They were maintained on a 12:12 h light:dark cycle. Grit and water were always available within their individual home cages. All experiments were conducted in accordance with the Institutional Animal Care and Use Committee (IACUC) of The College of Staten Island/CUNY.

2.2. Materials and apparatus

Dizocilpine maleate (*5-methyl-10,11-dihydro-5H-dibezo[a,d]-cyclohepten-5,10-imine maleate*) or MK-801 was obtained from Research Biochemicals, Inc. (Natick, MA). Subjects were administered MK-801 0.15 mg/kg i.p. or saline vehicle only, approximately 1 h prior to each session. In *Phase 1*, subjects were run for 30 sessions about two or three times a week based on weight over a 3-month period before a