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Research Report

# Kainate-activated currents in the ventral tegmental area of neonatal rats are modulated by interleukin-2

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**Abstract**

Interleukin (IL)-2 is a potent modulator of neurotransmission and neuronal development in the mesolimbic and mesostriatal systems. It is also implicated in pathologies (including schizophrenia, Parkinson's disease, autism, cognitive disorders) that are linked with abnormalities in these systems. Since the kainate receptor plays an essential role in mesolimbic neuronal development and excitability, we examined the effects of physiologically relevant concentrations of IL-2 on kainate-activated current ($I_{KA}$) in voltage-clamped neurons freshly isolated from the ventral tegmental area (VTA) of 3- to 14-day-old rats. IL-2 (0.01 – 10 ng/ml) alone had no effect on membrane conductance. When co-applied with kainate, IL-2 significantly decreased $I_{KA}$. IL-2 (2 ng/ml) shifted the kainate concentration – response curve to the right in a parallel manner, significantly increasing the $EC_{50}$ without changing the maximal $I_{KA}$. IL-2 inhibition of $I_{KA}$ was voltage-dependent, being greater at negative potentials. IL-2 did not alter the reversal potential. These findings suggest that IL-2 potently modulates kainate receptors of developing mesolimbic neurons. We suggest that IL-2 plays a role in the excitability of developing neurons in the mesolimbic system. Inasmuch as increased $I_{KA}$ is associated with excitotoxicity, coupled with the present observation that IL-2 inhibits $I_{KA}$, we suggest an adaptive role for IL-2 in limiting excitotoxicity in the developing brain. IL-2 might thus be required for normal cell development in the mesolimbic and mesostriatal systems.
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*Theme:* Endocrine and autonomic regulation
*Topic:* Neural – immune interactions

*Keywords:* Cytokine; Mesolimbic; Excitatory amino acid; Development; Neurotoxicity; Neurogenesis; Neurodevelopment; Dopamine; Schizophrenia; Autism

## 1. Introduction

Interleukin (IL)-2 is a 15 – 20 kDa glycoprotein that modulates central nervous system (CNS) activity [9]. IL-2 is present and modulates activity in the mesolimbic and mesostriatal systems. IL-2 mRNA and receptors are expressed in the cortex, mesencephalon, and striatum [9,19]. Furthermore, there is a functional relationship between IL-2 and dopamine activity in these regions. For example, IL-2 influences dopamine turnover in the medial prefrontal cortex [35] and dopamine release in the nucleus accumbens in vivo [2,14,24]. IL-2 also modulates $K^+$-, veratrine-, NMDA-, and kainate-induced dopamine release from mesencephalic and basal forebrain slices in developing and adult rats [1,15,20]. We also showed that IL-2 modulates NMDA-activated current in dopaminergic neurons of neonatal rats [31]. Typically, IL-2-induced alterations of transmitter release occur in a biphasic manner such that opposite effects are induced by low and high doses. Additionally, IL-2 influences behavioral responses that are

*Abbreviations:* $I_{KA}$, kainate-activated current; CNS, central nervous system; IL-2, interleukin-2

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associated with mesolimbic and striatal dopamine activity [14,18,20,25,33,34,36].

In addition to modulating neurochemical activity in the mesolimbic and striatal systems, IL-2 promotes the survival of neonatal cortical, striatal, and hippocampal cells [3,22], suggesting that it may be required for normal cell development in these areas. In support of this suggestion, IL-2 knockout mice display marked hippocampal abnormalities and cognitive deficits [21]. Further to the point, IL-2 is implicated in the etiology and pathogenesis of neurodevelopmental disorders (e.g., schizophrenia, autism) that are associated with aberrations in limbic and cortical structures. The mechanisms mediating these effects of IL-2, however, are not known.

The ventral tegmental area (VTA) is the site of origin of the mesolimbic system, a system involved in aspects of motivation, cognition, and the rewarding properties of drugs of abuse like ethanol [8,30]. The VTA contains dopaminergic and non-dopaminergic neurons [11,13]. The majority of cell bodies in this region are dopaminergic, the axon terminals of which release dopamine in target areas, notably the nucleus accumbens and prefrontal cortex [29]. Cell bodies in the VTA receive a monosynaptic innervation from prefrontal cortex and have *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors [26], and glutamatergic afferents from the hippocampus to the nucleus accumbens strongly excite VTA dopamine neurons [7].

In addition to NMDA receptor/channel activity, kainate receptor/channel regulates the excitability as well the firing pattern of VTA dopamine neurons and dopamine release [12,17,26,28,29]. Kainate (KA) receptors are a family of ionotropic glutamate receptors, which mediate the excitatory synaptic transmission in various areas of the mammalian CNS. A recent study on the expression pattern of the genes encoding for KA receptor subunits indicated that most of the transcripts for KA subunits change with development and may contribute to the establishment of the fine tuning of the excitatory circuits reciprocally established between CNS areas [16].

Inasmuch as the kainate receptor/channel plays an essential role in modulating neuronal excitability of developing mesolimbic neurons, coupled with the mentioned links between IL-2 and the mesolimbic system and related pathologies, we hypothesized that IL-2 modulates the excitability of VTA neurons, and that this modulation involves interactions with the kainate receptor/channel. Using the whole-cell patch-clamp technique, we demonstrate for the first time that IL-2 potently modulates the kainate receptor/channel of developing mesolimbic neurons.

## 2. Materials and methods

### *2.1. Isolation of neurons and electrophysiological recording*

The care and use of animals and the experimental protocol of this study were approved by the Institutional Animal Care and Use Committee of University of Medicine and Dentistry of New Jersey. We performed our experiments on VTA neurons prepared as described earlier [31]. Briefly, 5- to 14-day-old Sprague–Dawley rats were decapitated. The brain was quickly excised, placed into ice-cold saline saturated with 95% $O_2$ and 5% $CO_2$, glued to the chilled stage of a vibratome (Campden Instruments, UK), and sliced to a thickness of 300–400 μm. Slices were transferred to the standard external solution saturated with $O_2$, containing 1 mg pronase/6 ml and incubated (31 °C) for 20 min. After additional 20 min incubation in 1 mg thermolysin/6 ml, the VTA was identified medial to the accessory optic tract and lateral to the fasciculus retroflexus under a dissecting microscope. Micro-punches of the VTA were isolated and transferred to a 35 mm culture dish. Mild trituration of these tissue punches through heat polished pipettes of progressively smaller tip diameters dissociated single neurons. Within 20 min of trituration, isolated neurons attached to the bottom of the culture dish and were ready for electrophysiological experiments. Based on morphology under the light microscope, the cells acutely isolated from VTA could be divided into two types: bipolar and multipolar. The majority are bipolar, with 1–3 dendritic processes emerging from each end of the soma. The soma is fusiform in shape and from 20–40 μm in length and 15–25 μm in diameter. The multipolar neurons are larger with a diameter of 35–60 μm and have 4 to 5 major dendrites. Most of the cells are tyrosine hydroxylase-positive and therefore presumed to be dopaminergic. This is in good agreement with the recent reports [6,27]. There are no appreciable differences between these two groups of neurons regarding their response to ethanol. Thus, we recorded data from neurons of both shapes.

The saline in which the brain was dissected contained (in mM): NaCl 128, KCl 5, $NaH_2PO_4$ 1.2, $NaHCO_3$ 26, $MgCl_2$ 9, $CaCl_2$ 0.3, glucose 2.5. The standard external solution contained (mM): NaCl 140, KCl 5, $MgCl_2$ 1, $CaCl_2$ 2, glucose 10, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) 10. The pH was adjusted to 7.4 with Tris base and the osmolarity to 320 mM/kg with sucrose. The patch electrode had a resistance between 3 and 5 MΩ when filled with the solution contained (in mM): CsCl 120, TEA–Cl 21, $MgCl_2$ 4, 1, ethyleneglycol bis-(-aminoethylether)-*N,N,N′N′*-tetraacetic acid (EGTA) 11, $CaCl_2$ 1, HEPES 10, and Mg-ATP 2. The pH was adjusted to 7.2 with Tris base and the osmolarity to 280 mM/kg with sucrose. Throughout all experimental procedures, the bath was continuously perfused with the standard external solution. All kainate-induced responses were elicited in this solution at an ambient temperature of 20–23 °C.

Currents were recorded under voltage-clamp with an Axopatch 1D amplifier (Axon Instruments, Forster City, CA, USA) interfaced to a desktop computer via a Digidata 1200 (Axon Instruments) analog to digital converter and directly

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