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Research Report

CNQX facilitates inhibitory synaptic transmission in rat hypoglossal nucleus

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ABSTRACT

6-cyano-7-nitroquinoxaline-2, 3-dione (CNQX) is a most commonly used antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor in the central nervous system. During the past two decades, studies had demonstrated that CNQX could partially activate AMPA receptors that are located on the hippocampal and cerebellar interneurons, thus subsequently leading to the facilitation of inhibitory transmission. However, whether CNQX could enhance inhibitory synaptic transmission in the hypoglossal nucleus remains elusive. Here, using whole-cell patch-clamp recording in the brainstem slice, we showed that CNQX greatly increased both frequency and amplitude of spontaneous inhibitory postsynaptic currents in the hypoglossal motoneurons, whereas D-(-)-2-Amino-5-phosphonopentanoic acid (D-AP5), *N*-methyl-D-aspartate (NMDA) receptor antagonist, had no effect on inhibitory synaptic transmission. Application of bicuculline and strychnine further identified that CNQX not only increased GABAergic sIPSCs but also glycinergic one in these motoneurons. Similar enhancement of inhibitory transmission was observed with application of 6, 7-dinitroquinoxaline-2, 3-dione (DNQX), a quinoxaline derivative of CNQX, but not with application of GYKI 53655, a non-competitive antagonist of AMPA receptor. In the presence of tetradotoxin, the effect of CNQX on sIPSCs was

Abbreviations: CNQX, 6-cyano-7-nitroquinoxaline-2, 3-dione; ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; D-AP5, D-(-)-2-Amino-5-phosphonopentanoic acid; DNQX, 6,7-dinitroquinoxaline-2,3-dione; GABA, gamma-aminobutyric acid; HMs, hypoglossal motoneurons; NMDA, *N*-methyl-D-aspartate; TARP, transmembrane AMPA receptor regulatory protein; TTX, tetrodotoin

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abolished, suggesting that an increase in presynaptic interneuron spike firing rate induced by CNQX was responsible for the facilitation of sIPSCs. Taken together, these results demonstrated that the excitatory effect of CNQX on presynaptic interneurons triggered enhancement of both GABAergic and glycinergic synaptic transmission within the rat hypoglossal nucleus.

1. Introduction

The hypoglossal nucleus, where the overwhelming majority of neurons are cholinergic hypoglossal motoneurons (HMs) (Davidoff and Schulze, 1988; Viana et al., 1990), is suggested to provide a fundamental function in respiration, swallowing, suckling, and mastication (Sawczuk and Mosier, 2001). By coupling with each other through gap junction, HMs can directly innervate tongue muscles to accomplish the physiological functions through hypoglossal nerve. Coordination in the activity of these coupled HMs can generate rhythmic signal to guide genioglossus muscle, thereby is crucial for maintaining various functions in the upper airway. The output (*i.e.*, firing rates and burst patterns) of HMs can be modulated by either excitatory or inhibitory inputs projected from the other brain regions (Marchetti et al., 2002; Rekling et al., 2000). These neurons received excitatory glutamatergic inputs from the primary motor cortex and local reticular formation as well as inhibitory inputs from interneurons in the reticular formation adjacent to the hypoglossal nucleus (Li et al., 1996, 1997). Most of these inhibitory inputs are glycinergic in nature, whereas the other inhibitory components are GABAergic (O'Brien and Berger, 2001). Regulation of inhibitory synaptic transmission can affect respiratory rhythm by altering HMs membrane potential and changing the output pattern of HMs.

Previously, studies had investigated the isolation of spontaneous inhibitory neuronal activity within the central nervous system (CNS)

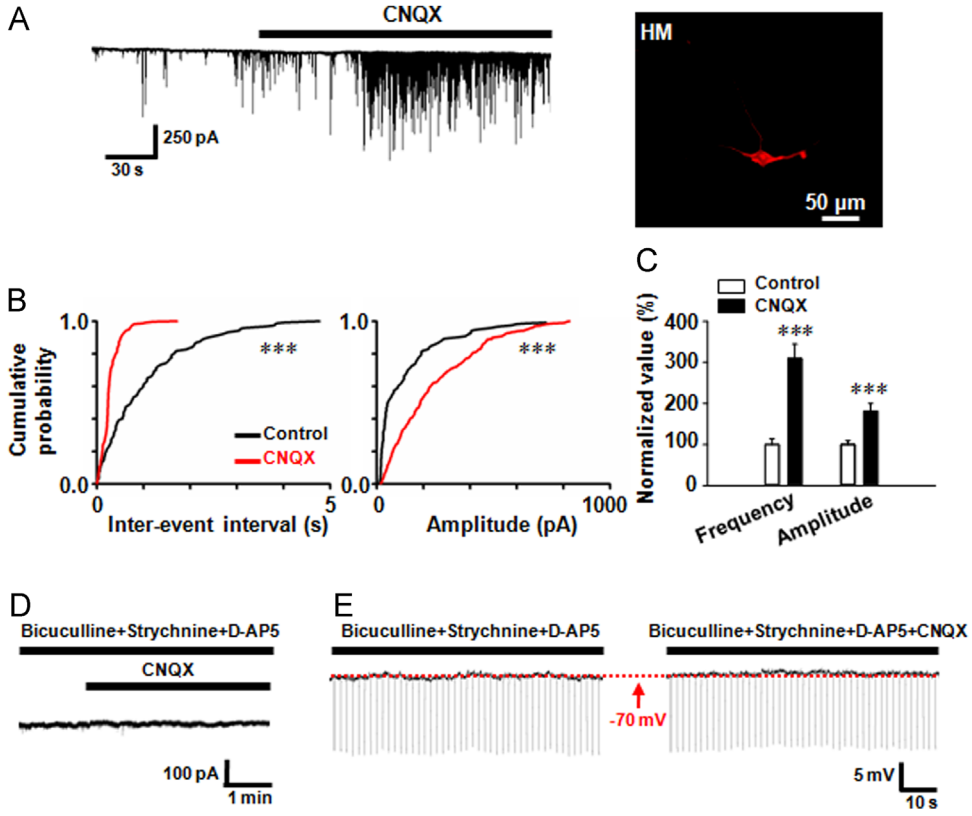

Fig. 1 – CNQX-induced potentiation of inhibitory synaptic transmission in hypoglossal motoneurons. (A) Left panel: sample trace of sIPSCs from a HM before and after perfusion of CNQX (10 μM). Noted that CNQX exerted a robustly increased spontaneous events. Right panel: photomicrograph of a recorded HM in the left panel, as labeled with neurobiotin. (B) Cumulative probability plot of inter-event interval and amplitude of sIPSCs from a sample neuron. The inter-event interval curve significantly shifted leftward with application of CNQX, whereas the amplitude curve significantly shifted rightward with application of CNQX. (C) Bar graph shows the effect of CNQX on the frequency and amplitude of sIPSCs. (D) No detectable inward or outward basal current was found in HM treated with CNQX. (E) CNQX did not change membrane potential and input resistance of HM. Voltage deflections were responses to periodic current injections of −100 pA for 100 ms at 0.5 Hz.