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Bilirubin enhances neuronal excitability by increasing glutamatergic transmission in the rat lateral superior olive

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Abstract

Hyperbilirubinemia is one of the most common clinical phenomena observed in human newborns. To achieve effective therapeutic treatment, numerous studies have been done to determine the molecular mechanisms of bilirubin-induced neuronal excitotoxicity. However, there is no conclusive evidence for the involvement of glutamatergic synaptic transmission in bilirubin-induced neuronal hyperexcitation and excitotoxicity. In the present study, using gramicidin-perforated patch-clamp techniques, spontaneous excitatory postsynaptic currents (sEPSCs) were recorded from lateral superior olive (LSO) neurons isolated from postnatal 11–14-day-old (P11-14) rats. The application of 3 μM bilirubin increased the frequency, but not the amplitude, of sEPSCs. The action of bilirubin was tetrodotoxin (TTX)-insensitive, as bilirubin also increased the frequency, but not the amplitude, of mEPSCs. The amplitudes of GABA-activated (I_{GABA}) and glutamate-activated (I_{glu}) currents were not affected by bilirubin. Under current-clamp conditions, no spontaneous action potentials were observed in control solution. However, the application of 3 μM bilirubin for 4–6 min evoked a considerable rate of action-potential firing. The evoked firing was partially occluded by D,L-2-amino-5-phosphonovaleric acid (APV), an NMDA receptor antagonist, but completely inhibited by a combination of APV and 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX), an AMPA receptor antagonist. These results indicate that bilirubin facilitates presynaptic glutamate release, enhances glutamatergic synaptic transmission by activating postsynaptic AMPA and NMDA receptors, and leads to neuronal hyperexcitation. This study provides a better understanding of the mechanism of bilirubin-induced excitotoxicity and determines for the first time that both AMPA and NMDA receptors are likely involved in the excitotoxicity produced by bilirubin.

Biography

Chunyan Li has completed her PhD at the age of 28 years from Shanghai Jiaotong University. She now is a doctor of Department of Otorhinolaryngology, Affiliated Sixth People's Hospital of Shanghai Jiaotong University. She has focused her research on the mechanism of bilirubin neurotoxicity in auditory centre system and published 9 papers in reputed journals such as Toxicology and Experimental neurology.