Abstract

The locus coeruleus (LC) is the major noradrenergic nucleus of the brain, containing ~50 % of all central noradrenergic neurons. From its location, laterally to the fourth ventricle in the dorsal-rostral pons, the neurons of the LC project throughout the entire CNS. This broad and complex network associates the LC with the control of many different behavioural and cognitive functions such as sleep, arousal, stress and attention. Many studies investigated the role of the LC in the regulation of sleep and arousal and could demonstrate that distinct activity patterns of the LC are associated with different states of sleep and arousal. The contribution of the LC to the regulation of sleep has been proposed to be in concert with nuclei of the serotonergic system. Similarly to the LC, the activity of the dorsal raphe nucleus have been shown to be associated to different states of sleep. Interestingly, the LC and dorsal raphe nucleus were found to innervate each other reciprocally. Furthermore, neurons of the LC are known to be inhibited by 5-hydroxytryptamin (5-HT). However, the physiological relevance of this connection is still not fully understood and the precise modulation of LC neurons intrinsic properties by 5-HT has not been investigated.

To unravel the physiological role of the LC and its modulation by 5-HT, it is crucial to understand the intrinsic electrophysiological properties of its neurons. In previous work, several electrophysiological properties of LC neurons have been characterised. However, there are three major reasons to revisit the characterisation of LC neurons: First, previous experiments were performed in rats, cats and monkeys. Yet, the mouse has become one of the most important model organisms for many biological disciplines. Second, most studies focused on the LC network or did not isolate neurons from network modulation. Third, the development of the perforated patch clamp technique enables recording without interfering with the cell intrinsic mechanisms.

For those reasons the perforated patch clamp technique was used on synaptically isolated LC neurons in mouse brain slices to characterise their intrinsic membrane properties. With such characterisation as baseline the modulation of LC neurons by 5-HT was investigated. In line with the literature, all recorded LC neurons generated a very regular spontaneous activity. Synaptic isolation did not disrupt this pacemaking but significantly increased the action potential (AP) frequency in all experiments. All recorded neurons showed a prolonged hyperpolarisation after sustained excitation which was strongly Ca^{2+} dependent. Furthermore, LC neurons showed a delayed excitation after hyperpolarisation that was strongly modulated by fast transient K^+ currents. Interestingly, the APs of LC neurons could be discriminated into at least two different types based on clear differences in the depolarisation rate and threshold.

The application of 5-HT modulates LC neurons of mice in a bi-directional manner. On one hand, 5-HT reduced the responsiveness to weak stimuli by hyperpolarising the membrane potential and decreasing the input resistance. On the other hand, 5-HT drastically increased the responsiveness since strong stimuli elicited more APs compared to control. The first effect is suggested to be mediated by the modulation of G-protein coupled K^+ channels. Occlusion experiments suggest that the latter effect is mediated by the modulation

of voltage activated Ca^{2+} channels and Ca^{2+} dependent K^+ channels. Accordingly, 5-HT reduced the Ca^{2+} transients elicited by AP bursts and modulated the current conducted by small conductance Ca^{2+} dependent K^+ channels. These results suggest a mechanism by which the signal-to-noise ratio and thereby the signal detection of individual neurons might be modulated. Most intriguingly, this mechanism is based solely on the direct modulation of intrinsic membrane properties of single neurons.

Taken together the in rats described electrophysiological characteristics of LC neurons could be confirmed for mouse LC neurons. However, the detailed analysis of APs revealed that the cell population of the LC might be more heterogeneous than previous electrophysiological studies indicate. Furthermore, the results confirm that 5-HT modulates LC neurons, but also suggest that the modulatory effects are more complex than previously thought.