

## Summary

Many experimental as well as clinical studies have shown that subcortical neuronal circuitries including the anterior part of the substantia nigra pars reticulata (SNR) are closely involved in the control of seizures propagation and termination. In vivo studies in rats demonstrated that inhibition of the GABAergic SNRA electrical output increases the seizure threshold in the flurothyl model of generalized clonic seizures. The anticonvulsant properties of the SNRA are largely age- and sex-dependent. In the current experiments were used 3 age groups of Sprague Dawley rats (PN5-9, PN11-16 and PN25-32 days, PN = postnatal) to study GABAergic inhibition. Two types of GABAergic inhibition were studied: a) a synaptic inhibition, which is generated by  $\alpha 1$  and  $\alpha 3$ -containing GABAARs and b) a tonic inhibition mediated by extrasynaptic  $\delta$  subunit-containing GABAARs. Immunohistochemistry showed that the  $\alpha 1$  subunit expression was generally more abundant in adult rats and females while the  $\alpha 3$  subunit dominated in the early development and gradually decreased by the age of PN30. The more  $\alpha 1$  subunit was expressed the faster were the kinetics, higher the mean amplitudes and frequencies of spontaneous inhibitory postsynaptic currents (sIPSCs). The  $\alpha$  subunit subtype underlies sensitivity to zolpidem, which preferentially acts via the  $\alpha 1$  subunit. The extrasynaptic  $\delta$  subunit was present equally in males and females but its expression was markedly higher in early maturational stages and decreased later on. As a result, the tonic GABA inhibition measured as a BIM-sensitive current was highest in youngest animals and lowest in older ones. However, a THIP-induced tonic current (a GABAARs 72 agonist acting via  $\alpha 4\beta 3\delta$  subunits) did not entirely parallel the  $\delta$  subunit expression as no age-related differences were found. PN5-9 males were more sensitive to THIP than the same age females. A muscimol-generated tonic current (a GABAARs agonist preferentially acting via  $\alpha 1$  subunit) was maximal in older rats and prevailed in females, which can be explained by abundance of the  $\alpha 1$  subunit at this age and sex. Zolpidem ability to elicit a small inward current in SNR neurons signifies that also non- $\delta$  subunit GABAARs mediate a tonic current. Knowledge of sex- and age-related differences in GABAergic transmission in the SNRA is an important precondition to develop more potent antiepileptic drugs for treatment refractory seizures.