**Effect of cytochrome P450 inhibition by proadifen on the excitability of central monoamine-secreting neurons in rats**

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Cytochrome-P450 (CYP) is a superfamily of microsomal and mitochondrial enzymes which catalyze oxidation of various biological molecules, such as steroids. CYP irreversibly metabolizes corticosterone into 6β-corticosterone in rodents and cortisol into 6β-cortisol in humans. Central monoamine transmission regulates hepatic glucocorticoid metabolism, and vice versa. Central 5-HT negatively, and norepinephrine-positively modulates CYP expression and activity in the liver. The effect of glucocorticoids on brain monoamine concentrations is depending on the brain area. For instance, chronic stress increases thalamic 5-HT and decreases hypothalamic dopamine, *via* a mechanism putatively involving glucocorticoids. In this study, we aimed to investigate the effect of CYP inhibition on in vivo excitability of rat serotonin (5-HT) neurons of the dorsal raphe nucleus (DRN), norepinephrine neurons of the locus coeruleus (LC), and dopamine neurons of the ventral tegmental area (VTA). Adult male Wistar rats (200–250 g.) were used in experiments. A CYP inhibitor proadifen (SKF525) was administered intraperitoneally (i.p.), 25 mg/kg, 49, 25, and one hour before electrophysiological assessments. Control animals were injected saline using the same protocol. Rats were anesthetized with chloral hydrate (0.4 g/kg, i.p.) and glass electrodes were stereotaxically inserted into the DRN, LC, or VTA. The spontaneously active 5-HT, norepinephrine, and dopamine neurons were recognized according to their firing pattern. We found a significant (p<0.05, two-tailed Student’s t-test) ~20% decrease in 5-HT neuronal firing activity in SKF525-administered rats, in comparison with controls. SKF525 did not alter the excitability of norepinephrine-secreting neurons of the LC. The mean firing rate of dopamine-secreting neurons was however significantly (p<0.05) increased by SKF525 treatment (130% of controls). As a potent inhibitor of glucocorticoid metabolism by CYP, SKF525 increases plasma concentration of these hormones. On the other side, glucocorticoids inhibit the excitatory glutamatergic input to 5-HT neurons of the DRN. It is therefore possible that corticosterone mediates, at least in part, the inhibitory effect of SKF525 on brain 5-HT neurons. Since the excitability of dopamine neurons is negatively regulated by serotonin, the increase in dopamine neuronal firing activity might be secondary to the SKF525-induced inhibition of 5-HT tone. Modulation of excitability of 5-HT and dopamine neurons by glucocorticoids might be thus an important element in the interaction between glucocorticoid and monoamine signaling. This study was funded by Slovak Research and Development Agency *via* the contract APVV-19-0460 and by Scientific Grant Agency of Ministry of Education of Slovak Republic and Slovak Academy of Sciences *via* the grant VEGA 2/0046/18.