Nitric oxide (NO) modulates a variety of processes in the mammalian brain, but the mechanisms of neuronal NO signaling are poorly understood. In the periphery, many effects of NO are mediated via the generation of the second messenger cyclic guanosine-3',5'-monophosphate (cGMP) and activation of the cGMP-dependent protein kinase type I (cGKI). However, previous studies suggested that the expression of cGKI in the nervous system is rather restricted, thus, questioning the functional significance of the cGMP/cGKI pathway as a mediator of NO signaling in the brain. Here we have performed a detailed immunohistochemical study to elucidate the distribution of cGKI in the CNS and eye of the mouse. Expression of cGKI protein was detected not only in the previously described areas (cerebellum, hippocampus, dorsomedial hypothalamus) but also in a number of additional regions, such as medulla, subcommissural organ, cerebral cortex, amygdala, habenulae, various hypothalamic regions, olfactory bulb, pituitary gland, and retina. Immunoblotting with isoform-specific antibodies indicated that the cGKIA isoform is prominent in the cerebellum and medulla, whereas the cGKIB isoform is predominant in the cortex, hippocampus, hypothalamus, and olfactory bulb. Similar levels of the isoforms were detected in the pituitary gland and
eye. Thus, it appears that distinct brain regions express distinct cGKI isoforms that signal via distinct pathways. Together, these results improve our understanding of the cellular and molecular mechanisms of NO/cGMP/cGKI signaling and indicate that the distribution and functional relevance of this pathway in the mammalian brain is broader than previously thought.