The elucidation of the roles of GABA in the control of blood pressure: analysis using genetically engineered mice

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Summary

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system. GABA is produced by glutamate decarboxylase (GAD), which has two isoforms (GAD65 and GAD67) encoded by separate genes. We have determined the structure of mouse GAD65 and GAD67 genes and analyzed their promoters using transgenic mice. Several studies have suggested that a GABA deficit in the caudal hypothalamus of the spontaneously hypersensitive rat contributes to elevated levels of arterial pressure. To further elucidate the role of GABA in the control of blood pressure, we have generated mice in which GAD65 was targeted by homologous recombination. GAD65 proteins were not detected in the brain of homozygous GAD65 mutants by Western blot analysis.

Systolic blood pressure and heart rate measurements in conscious mice by using tail cuff method showed an average systolic pressure of 98 $\pm$ 3 mmHg (n = 6) and 105 $\pm$ 4 mmHg (n = 6) in wild-type and GAD65 knockout mice, respectively ($P > 0.05$). Heart rates averaged 569 $\pm$ 39 beats/min (n = 6) and 635 $\pm$ 19 beats/min (n = 6) in wild-type and GAD65 knockout mice, respectively ($P > 0.05$). On the other hand, locomotor activity in GAD65 knockout mice was significantly increased relative to that in wild-type mice. These results suggest that both GAD65 and GAD67 proteins, but not only GAD65, might be involved in the control of blood pressure. Conditional GAD67 knockout mice will be useful for elucidating the functional role of GABA in the control of blood pressure.