

## **The role of CAPON-mediated hypothalamic nNOS-NO system in the pathogenesis of depression**

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### Research question and background

The dysfunction of hypothalamo–pituitary–adrenal (HPA) axis that initiated by the hyperactivity of corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) plays an important role in the pathogenesis of stress and depression. Nitric oxide (NO) is crucial for the regulation of HPA axis activity. There are at least three types of NO synthase, namely inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal NOS (nNOS). nNOS is the primary source of NO in the central nervous system. CAPON is an adapter protein for nNOS and exerts negative regulation on the nNOS activity. We found an up-regulation of CAPON and a down-regulation of nNOS in the prefrontal cortex (PFC) of depressed patients and a significant reduction of nNOS in the hypothalamic PVN of Chronic Unpredicted Stress (CUS) rats. However, it is largely unknown about the exact mechanism that CAPON-mediated nNOS activity regulation participates in stress and depression.

### Methods and tissues used

Immunocytochemistry and double immunofluorescence were used to investigate the distribution of CAPON and the colocalization of nNOS with CAPON and PSD-95 in the medial PFC (mPFC), the anterior cingulate cortex (ACC) and the hypothalamic PVN of depressed patients. Western blot, co-immunoprecipitation and behavior tests were used to observe the effects of specially down-regulating CAPON expression on the nNOS-NO system, HPA axis activity and anxiety/depression behaviors in CUS rats. In addition, brain slice electrophysiology was used to detect the effects of CAPON down-regulation on the GABA-mediated synaptic activity in the hypothalamic parvocellular neurons.

### Results and conclusion

This project has just begun, with the purpose of elucidating the molecular mechanism by which the CAPON-mediated hypothalamic nNOS-NO system down-regulation promotes stress and depression. We expect to provide scientific evidence for the research and application of those antidepressants targeting nNOS adapter proteins.