

Cholinergic Immunolesioning Produced Tangle-like Inclusions *(continued from page 1)*

synthase kinase 3-beta (GSK3 β)-, protein kinase A (PKA)-, and extracellular signal-regulated kinase (ERK2) of the ERK-mitogen-activated protein kinase (MAPK) cascade. This leads to reduced phosphorylation of cAMP responsive element binding protein (CREB) that results in synaptic and memory deficits much earlier than the emergence of classic AD pathology. Thus, subtly elevated A β , together with BFCN deficits resulting from A β -induced deranged signaling, set up a vicious feedback loop to produce characteristic plaque and tangle pathology observed in AD.

Based on these facts, we wished to test if selective lesioning of BFCN during the early stages of amyloid build-up exacerbate tau phosphorylation and produce tangle-like inclusions in transgenic mice with APP mutations. We produced selective immunotoxic lesions of BFCN by injecting the BFCN-specific cholinergic immunotoxin, mu p75-SAP (Cat. #IT-16) which is known to specifically target p75-expressing BFCN. This specific targeting agent was administered intracerebroventricularly in TgCRND8 mice harboring Swedish (KM670/671NL) and Indiana (V717F) mutations. The resulting model exhibited tangle-like inclusions, provoked already existing plaque pathology, and worsened impaired behavioral deficits. The combination of the transgenic mice treated with the immunotoxin provides a powerful tool for understanding AD progression.

Targeting Topics: Recent Scientific References

(continued from page 4)

Long-term effects of neonatal basal forebrain cholinergic lesions on radial maze learning and impulsivity in rats.

Scattoni ML, Adriani W, Calamandrei G, Laviola G, Ricceri L
Behav Pharmacol 17(5-6):517-524, 2006.

Work in the last decade has focused on clarifying the role of cholinergic dysfunction in Alzheimer's disease. Seven-day-old rats received 0.21 μ g of 192-IgG-SAP (Cat. #IT-01) administered to the third ventricle, and were tested at 5 months of age in delay tolerance and radial maze. Test results suggest that prolonged basal forebrain cholinergic hypofunction is detectable only during highly complex tasks.

An activity-dependent assay for ricin and related RNA N-glycosidases based on electrochemiluminescence.

Keener WK, Rivera VR, Young CC, Poli MA
Anal Biochem 357(2):200-207, 2006.

The authors use synthetic biotinylated RNA substrates to assay adenine-specific RNA N-glycosidases, one of which is saporin (Cat. #PR-01). The RNA substrates are annealed to a ruthenylated oligodeoxynucleotide, allowing the capture of ruthenium chelate on magnetic beads. The N-glycosidase activity can then be detected by enzyme-linked chemiluminescence. The developed assay provides a robust

method for assessing threats involving N-glycosidases.

Neurotoxic lesions centered on the perifornical hypothalamus abolish the cardiovascular and behavioral responses of conditioned fear to context but not of restraint.

Furlong T, Carrive P
Brain Res [Epub Nov 24], 2006.

This work examined the role of orexin-containing neurons in the perifornical hypothalamus (PeF) during stress response. Orexin-SAP (Cat. #IT-20) or the control conjugate Blank-SAP (Cat. #IT-21) was injected into the PeF of pre-conditioned rats. Tests measuring restraint and conditioned fear to context were then performed on the lesioned animals. While the lesioning was not specific enough to connect results to orexin-containing neurons, the data indicate that the PeF is critical for some forms of stress, but not others.

Role of catecholaminergic neurons of the caudal ventrolateral medulla in cardiovascular responses induced by acute changes in circulating volume in rats.

Pedrinio GR, Maurino I, de Almeida Colombari DS, Cravo SL
Exp. Physiol 91(6):995-1005, 2006.

Catecholaminergic neurons in the caudal ventrolateral medulla (CVLM) are thought to help regulate body fluid

homeostasis and cardiovascular response due to changes in circulating volume.

The authors injected 6.3 ng of anti-DBH-SAP (Cat. #IT-03) into the CVLM of rats, and measured several physiological parameters following an injection of hypertonic or isotonic saline. Data from the lesioned rats indicate that catecholaminergic neurons mediate the cardiovascular response to volume expansion or increases in sodium levels.

Effect of selective cholinergic denervation on the serotonergic system: implications for learning and memory.

Garcia-Alloza M, Zaldua N, Diez-Ariza M, Marcos B, Lasheras B, Javier Gil-Bea F, Ramirez MJ
J Neuropathol Exp Neurol 65(11):1074-1081, 2006.

The authors compared two lesioning methods using 192-IgG-SAP (Cat. #IT-01) to examine the role of the serotonergic system in learning and memory. Administration of 0.067 μ g of conjugate to each hemisphere of the nucleus basalis of Meynert reduced cholinergic markers in the frontal cortex. One μ g of conjugate administered to the ventricle of each hemisphere reduced cholinergic markers in the frontal cortex and hippocampus. Both models reduced serotonin levels in the frontal cortex, but only the ICV injections modified learning.