Neuropeptide Y

Richard E. Mains, Betty A. Eipper

NPY, acting through multiple receptors, plays an essential role in depression, alcoholism and regulation of food intake. Neuropeptide Y, a 36-residue amidated peptide and one of the most abundant peptides in the CNS, is expressed in many brain regions (Colmers et al., 1988). NPY was identified by screening for peptides with a COOH-terminal α-amide group; it was named NPY because it has a Tyrosine residue (Y) at the NH_2-terminal and a Y-amide at the COOH-terminal (Tatemoto, et al., 1982). Receptors for NPY are particularly abundant in the amygdala, hippocampus, hypothalamus, locus coeruleus, striatum, and cortex (Eaton et al., 2007). Humans have five NPY receptors, all of which are GPCRs. Studies with synaptosomes and electrophysiological slice recordings established that NPY, acting through its Y5 receptor, can reduce glutamate release from presynaptic terminals by activating c-Jun Kinase (Jnk) and reducing Ca^{2+} influx into presynaptic terminals (**Figure**) (Colmers et al., 1988; Whittaker et al., 1999; Pellieux et al., 2000). When NPY is increased in the hippocampus of rats, using a viral overexpression system, spatial learning is impaired and long-term potentiation is decreased (Sorensen et al., 2009). In addition, performance in spatial learning tasks is adversely affected. When rats with elevated hippocampal NPY are subjected to electrical stimulation resulting in seizures, seizure sensitivity is normal with elevated NPY, but seizure severity is dramatically reduced (Sorensen et al., 2009).

In human subjects, impaired NPY signaling is believed to be involved in anxiety, depression, alcoholism, schizophrenia, and post traumatic stress disorder (Eaton et al., 2007). Single nucleotide polymorphisms (SNPs) in the human NPY gene which lower NPY peptide levels are associated with depression and alcoholism (Eaton et al., 2007). SNPs in the NPY Y2

and Y5 receptors are strongly associated with alcohol dependence and alcohol withdrawal symptoms, notably seizures (Wetherill et al., 2008; Ciccocioppo et al., 2009). In addition, the NPY receptor SNPs are associated with strong tendencies for comorbidity of alcohol and cocaine dependence. There is decreased NPY in the cerebrospinal fluid of depressed patients and patients with anxiety syndromes (Eaton et al., 2007). As a consequence, orally active, brain penetrant antagonists specific for the NPY Y1 and Y5 receptors are being tested in various psychiatric trials (MacNeil, 2007).

In addition to psychiatric and substance abuse effects, NPY is orexigenic, strongly stimulating food intake (MacNeil, 2007). Some human trials have shown modest, but significant, weight loss with antagonists to the NPY Y5 receptor (MacNeil, 2007; Erondu et al., 2006). Now, combination therapy trials using multiple NPY receptor antagonists along with an endocannabinoid antagonist (endocannabinoids are also orexigenic) are being tested in human subjects (Zhang et al., 2010).

References

Ciccocioppo, R., Gehlert, D. R., Ryabinin, A., Kaur, S., Cippitelli, A., & Heilig, M. (2009). Stress-related neuropeptides and alcoholism: CRH, NPY, and beyond. *Alcohol*, *43*, 491–498.

Colmers, W. F., Lukowiak, K., & Pittman, Q. J. (1988). Neuropeptide Y action in the rat hippocampal slice: Site and mechanism of presynaptic action. *The Journal of Neuroscience*, *8*, 3827–3837.

Eaton, K., Sallee, F. R., & Sah, R. (2007). Relevance of Neuropeptide Y (NPY) in Psychiatry. *Current Topics in Medicinal Chemistry*, *7*, 1645–1659.

Erondu, N., Gantz, I., Musser, B., Suryawanshi, S., Mallick, M., & Heymsfield, S. B. (2006). Neuropeptide Y5 receptor antagonism does not induce clinically meaningful weight loss in

overweight and obese adults. *Cell Metabolism*, *4*, 275–282.

MacNeil, D. J. (2007). NPY Y1 and Y5 Receptor Selective Antagonists as Anti-Obesity Drugs. *Current Topics in Medicinal Chemistry*, *7*, 1721–1733.

Pellieux, C., Sauthier, T., Domenighetti, A., Marsh, D. J., Palmiter, R. D., Brunner, H. R., et al. (2000). Neuropeptide Y (NPY) potentiates phenylephrine-induced mitogen-activated protein kinase activation in primary cardiomyocytes via NPY Y5 receptors. *Proceedings of the National Academy of Sciences U.S.A.*, *97*, 1595–1600.

Sorensen, A. T., Nikitidou, L., Ledri, M., Lin, E. J. D., During, M. J., & Kokaia, M. (2009). Hippocampal NPY gene transfer attenuates seizures without affecting epilepsy-induced impairment of LTP. *Experimental Neurology*, *215*, 328–333.

Tatemoto, K., Carlquist, M., & Mutt, V. (1982). Neuropeptide Y, a novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide. *Nature*, *296*, 659–660.

Wetherill, L., Schuckit, M. A., Hesselbrock, V., Xuei, X., Liang, T., & Foroud, T. (2008). Neuropeptide Y receptor genes are associated with alcohol dependence, alcohol withdrawal phenotypes, and cocaine dependence. *Alcoholism: Clinical and Experimental Research*, *32*, 2031–2040.

Whittaker, E., Vereker, E., & Lynch, M. A. (1999). Neuropeptide Y inhibits glutamate release and long-term potentiation in rat dentate gyrus. *Brain Research*, *827*, 229–233.

Zhang, L., Lee, N. J., Nguyen, A. D., Enriquez, R. F., Herzog, H., & Sainsbury, A. (2010). Additive actions of the cannabinoid and neuropeptide Y systems on adiposity and lipid oxidation. *Diabetes, Obesity & Metabolism*, *12*, 591–603.