VIP–PACAP 2010: My Own Perspective on Modulation of Cognitive and Emotional Behavior

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Editorial: From the Desk of the Editor-in-Chief

This editorial focuses on cognitive and emotional behavior in relation to vasoactive intestinal peptide (VIP; Said and Mutt 1972), pituitary adenylate cyclase activating polypeptide (PACAP; Arimura 1992), and our original discovery of the VIP-regulated activity-dependent neuroprotective protein (ADNP) and its peptide derivative, drug candidate NAP (NAPVISQP, generic name davunetide; Bassan et al. 1999; Gozes et al. 2009).

About 20 years ago we showed that *in vivo* inhibition of VIP by a hybrid peptide antagonist resulted in reduced sexual/social interactions (Gozes et al. 1989) and impairment of diurnal rhythms (Gozes et al. 1995). The hybrid VIP antagonist potently inhibited VIP-associated cyclic adenosine monophosphate (cAMP) formation and VIP-related neuroprotection in cell cultures (Gozes et al. 1991). Following intracerebral administration in rats, this VIP antagonist and the external envelope glycoprotein (gp120) of the human immunodeficiency virus produced similar retardation of spatial discrimination (Glowa et al. 1992), suggesting that both impair memory for spatially related stimulus control. We have further shown that this impairment was ameliorated by VIP treatment, implicating VIP as a protective factor against dementia related to the acquired immunodeficiency syndrome (Glowa et al. 1992). We next showed that modulating VIP gene activity by genetic manipulations resulting in reduced peptide expression, leads to spatial memory impairment in mice (Gozes et al. 1993). Conversely,

in a rat model of Alzheimer's disease, we demonstrated that intranasal administration of VIP analogues improved cognitive behavior and protected against cholinotoxicity (Gozes et al. 1996; Gozes et al. 1999).

Our more recent studies followed the VIP-regulated ADNP and its peptide derivative NAP (NAPVISQP; Bassan et al. 1999) and showed that ADNP knockout was embryonic lethal at the time of brain formation (Mandel et al. 2007; Pinhasov et al. 2003). We then demonstrated that partial ADNP deficiency (ADNP^{+/-}) resulted in cognitive and social impairments that were coupled to tauopathy, a major pathology in Alzheimer's disease and frontotemporal dementia (Vulih-Shultzman et al. 2007). In the ADNP-deficient model (Vulih-Shultzman et al. 2007) as well as in models of Alzheimer's disease (Matsuoka et al. 2007; Matsuoka et al. 2008) and frontotemporal dementia (Shiryaev et al. 2009), we showed that intranasal administration of NAP ameliorated spatial memory impairments and inhibited tau-related pathology. It is interesting to note that ADNP and its related protein ADNP2, proteins that are important for cellular viability (Kushnir et al. 2008) are both expressed in the human hippocampus (Bassan et al. 1999; Dresner et al. 2010; Zamostiano et al. 2001) that is associated with short-term memory and Alzheimer's disease pathology. Importantly, our most recent studies show that ADNP/ADNP2 expression is deregulated in the hippocampus of schizophrenia patients (Dresner et al. 2010). Furthermore, intranasal NAP treatment protects against learning and memory impairments in a mouse model associated with cytoskeletal dysfunctions that are related to schizophrenia (Merenlender-Wagner et al. 2010).

The above studies have been translated into human clinical trials (Allon Therapeutic Inc.) demonstrating that NAP (generic name, davunetide; Gozes et al. 2009) improves cognitive scores in a patient population suffering from amnesic mild cognitive impairment (Markesbery et

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al. 2006; Petersen et al. 2006) that has been associated with tauopathy (Schmechel et al. 2008; Gozes et al. 2009); NAP (davunetide) also improved functional capacity in schizophrenia patients (Javitt 2010) and is being developed for treatment of the tauopathy, progressive supranuclear palsy.

Turning back to VIP, the VIP-related peptide, PACAP (Arimura 1992) also regulates ADNP (Nakamachi et al. 2006; Nakamachi et al. 2008; Zusev and Gozes 2004). At least three receptors for PACAP and VIP have been identified. The PACAP-specific receptor, PAC1 receptor, exhibits a higher affinity for PACAP than VIP, whereas VIP receptors, VPAC1 and VPAC2, have similar affinities for PACAP and VIP (Hamar et al. 1998). VPAC2 has been associated with VIP regulated ADNP expression in astrocytes (Zusev and Gozes 2004). While alternative splice variants of the PAC1 receptor have been associated with VIP neuroprotective activity (Pilzer and Gozes 2006). Interestingly, a peptide mixture including NAP and the related peptide SALLRSIPA induced increases in VIP mRNA, suggesting potential feedback regulation (Spong et al. 2002).

VIP and PACAP show tight association with the regulation of cognitive and emotional functions as detailed in the current issue of the Journal of Molecular Neuroscience.

For example, MacDonald and colleagues review here the involvement of the PACAP/VIP system in synaptic transmission in the hippocampus focusing on PACAP/VIP signaling through different pathways to regulate NMDA receptors in CA1 pyramidal cells. They review the activation of VPAC1 and VPAC2 that increases evoked NMDA currents via the cAMP/PKA pathway. They further review the activation of the PAC1 receptor that stimulates a PLC/PKC/Pyk2/Src signaling pathway to enhance NMDA receptor function in hippocampal neurons. Importantly, they show that different concentrations of PACAP induce different effects on the both AMPA-evoked current and basal synaptic transmission by activating different receptors. The effects of the VIP–PACAP signaling pathways in learning and memory are also reviewed in using transgenic mice and pharmacological methods.

Regarding emotional behavior, Hammack et al. (corresponding author, May) review the roles for PACAP expression and signaling in the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala as critical structures mediating fear- and anxiety-like behavior. These brain areas organize coordinated fear- and anxiety-like behavioral responses as well as peripheral stress responding to threats via projections to the paraventricular nucleus of the hypothalamus and brainstem regions. They show that BNST PACAP as well as PAC1 are up-regulated following chronic stress and suggest an interaction with the corticotropin-releasing hormone to mediate stress-associated behaviors, including anorexia and anxiety. These studies provide important therapeutic strategies for stress- and anxiety-management.

As highlighted by Lubics and colleagues, in vertebrates, PACAP has been shown to be involved in associative learning but it is not known if it plays a similar role in invertebrates. In an original study, they have now investigated the expression and biochemical roles of PACAP and receptors in the central nervous system of the pond snail *Lymnaea stagnalis*, one of the best established invertebrate model systems to study the molecular mechanisms of learning and memory. Using MALDI-TOF and immunohistochemistry, they established the presence of the 27 amino acid, PACAP-27 peptide in the cerebral ganglia and the lip region of *Lymnaea* and a 38 amino acid homologue, squid PACAP-38. They also showed that PACAP and VIP specifically stimulated the synthesis of cAMP in *Lymnaea* cerebral ganglion homogenates.

As cAMP and related pathways are closely associated with memory formation and storage (Kandel and Schwartz 1982) and as neuroprotection is essential for brain function, VIP and PACAP are placed at center stage with regards to the essence of learning and memory.

The current editorial is just touching the tip of the iceberg, citing only part of my own publications related to learning and memory, while not discussing others (e.g. Goldberg et al. 2009; Visochek et al. 2005). Obviously, there are many more publications in the field and much required future research aiming to uncover the intricate molecular basis of cognitive and emotional behavior. This selective review on VIP–PACAP–ADNP–NAP that highlights the current issue of the Journal of Molecular Neuroscience paves the path to new and original research. Our additional comprehensive reviews are accessible for perspective reading (Gozes 2007, 2008; Gozes 2010; Gozes and Brenneman 1989; Gozes et al. 2005; Gozes et al. 2009). New and exciting findings will be presented at the forthcoming VIP–PACAP and related peptides meeting in Eilat, Israel, 2011.

Disclosure I. Gozes serves as the Chief Scientific Officer, Allon Therapeutics Inc., Vancouver, BC, Canada.

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