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Functions of arginine vasopressin and its receptors: Importance of human molecular genetics studies in bidirectional translational research

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The paper by Maher, Vanyukov and colleagues is an extensive study of two cohorts phenotyped with a common liability of substance abuse disorders that reports an association of an arginine vasopressin (AVP) 1A receptor gene variant with these disorders (1). The AVP1A receptors are located throughout the brain and function in many roles, especially in stress responsivity. In contrast, the AVP1B receptors are located on corticotropes in the anterior pituitary and work primarily as part of the activating system of the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis by driving the processing and release of the constitutive peptides, ACTH and beta-endorphin, of proopiomelanocortin (POMC), of particular interest for the field of addictive diseases. The AVP1B receptor acts in parallel to the CRF-R1 receptor, where corticotropin releasing factor (CRF) acts to similarly drive the processing and release of POMC peptides of the HPA axis.

In our very earliest studies on the development of a pharmacotherapy to treat opiate dependency (specifically our studies to use methadone, which we hypothesized and later showed was a long-acting, mu opioid receptor selective agonist), when we ascended the dose of methadone too rapidly towards the “blockading doses,” in an attempt to prepare our subjects for studies of opioid cross-tolerance, we identified the modest adverse effect of excessive release of AVP (“ADH”), as evidenced clinically by mild “water intoxication” (2). This side-effect was completely prevented by ascending the dose of methadone more slowly, but taught us that methadone activates the release of AVP. Also in an early study, Inturrisi with Fujimoto showed that in rat models, morphine causes release of AVP, and with continued morphine administration, tolerance develops to this effect (3).

The role of AVP in activating the HPA axis was well-appreciated by the 1970s. Recent studies in rodent models and humans have been performed primarily with CRF since its elucidation and purification; CRF plays a similar role to AVP in the anterior pituitary. In our earliest human molecular genetics work, we were interested in the possible role of AVP1A and AVP1B receptors in specific addictive diseases. In 2009, we first reported an association of a different variant of the AVP1A receptor with severe long-term heroin addiction in African Americans (4). We have been rigorously re-exploring the role of AVP and its

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receptors in rodent models and, very recently, have reinitiated basic clinical research studies of AVP.

We think this human molecular genetics paper, which extends our earlier findings, as well as those of the Weinberger group, where the relationship of the AVP1A receptor with amygdala activation and personality traits relevant for drug abuse disorders were reported and related to autism, is important for the field (5). It is extremely important to determine whether identified variants that are shown to be associated with an addiction or other disease should be studied further for their functionality, such as we have done following our discovery of the A118G variant of the mu opioid receptor (6, 7). We found this variant to be associated with both opiate addiction and alcoholism, and to alter stress responsivity in healthy humans; it also predicts a positive response to naltrexone treatment in alcoholics (7).

AVP1A and 1B receptors in the CNS are expressed in rat extended amygdala, with high concentrations in nucleus accumbens, bed nucleus of stria terminalis (BNST) and central nucleus of amygdala. The neuropeptides, AVP and oxytocin, affect individual differences in social recognition and anxiety-related behaviors. Social behaviors have been shown to influence the risk for substance abuse. AVP1A receptors are found to play a prominent role in modulation of social behavior in male animal models (8).

Neuroanatomical distribution of AVP1B receptors is also in amygdala, hypothalamus, anterior pituitary, and hippocampus. Recent evidence suggests that increased AVP neuronal activity via AVP1B receptor represents an important step in the neurobiology of stress-related behaviors in several rodent models. Evidence has emerged implicating that AVP is physiologically involved in central reinforcing processes of addiction. Reduction of the number of AVP-immunoreactivity neurons and AVP mRNA levels in the paraventricular nucleus (PVN) of hypothalamus or BNST after chronic alcohol consumption has been demoted in humans and rats. We reported that amygdalar AVP gene expression levels were increased in acute heroin withdrawal; a systemically active, highly selective, non-peptide AVP1B receptor antagonist dose-dependently blocked stress-induced reinstatement of heroin-seeking behavior (9). Using genetically selected Sardinian alcohol-preferring rats, we found that pharmacological blockade of AVP1B receptor attenuated alcohol drinking (10). Together, these data suggest that the AVP1B system may be a critical component of neural circuitry contributing to drug withdrawal, drug-seeking and -taking behaviors.

Stress can increase the secretion of CRF and AVP into the pituitary portal circulation from terminals of the parvocellular division of PVN (pPVN), and AVP potentiates CRF-induced ACTH secretion from anterior pituitary into circulation. Although earlier studies have shown that AVP did not contribute to the acute stimulatory effects of cocaine on HPA activity, we predicted that the pPVN AVP is involved in modulation of HPA activity after chronic cocaine or its withdrawal. From acute to protracted (1 to 14-day) withdrawal from chronic escalating-dose “binge” cocaine administration, we found persistent elevations of both plasma ACTH levels and AVP mRNA levels in the PVN of rats. Selective AVP1B receptor antagonists attenuated cocaine withdrawal-induced HPA activation. Utilizing AVP-EGFP promoter transgenic mice, we found that protracted cocaine withdrawal increased the number of AVP-EGFP neurons in the parvocellular (but not magnocellular) division, suggesting that enhanced AVP gene expression is associated with persistent elevations of basal HPA activity, and indicating that the AVP1B receptor may be a therapeutic target for treating anxiety and depressive symptoms associated with drug addiction (11).

In humans, *AVP* and *OXT* (oxytocin) loci are closely linked at chromosome 20p13. They have similar intron-exon structure, their resultant peptides differ by two amino acids; they are thought to have a common ancestral gene. The *AVP* gene encodes a precursor protein

consisting of AVP and two associated proteins. AVP acts as a hormone regulating water balance in the periphery; several mutations in *AVP* were shown to cause diabetes insipidus. A correlation was found between CSF AVP levels and aggression in individuals with personality disorders. Association between an *AVP* haplotype and childhood-onset mood disorders has been reported.

Humans express three subtypes of AVP receptors: 1A, 1B and 2. Although all three of these proteins are 7 transmembrane domain G-protein coupled receptors, activation of AVP1A and 1B receptor stimulate phospholipase C, whereas activation of AVP2 receptor stimulates adenylate cyclase. The AVP2 receptor is expressed primarily in kidneys and will not be discussed further. The human *AVPR1A* gene is located at chromosome 12q14–15 and contains two exons. The 5′ flanking region contains three repeats: [GT]₂₅, RS1, and RS3. Various studies have linked different lengths of these repeats to behavioral traits suggesting that they are relevant for brain function related to emotional arousal and social behavior. Subjects with shorter RS3 have been reported to show less altruistic behavior. Several *AVPR1A* promoter SNPs were reported to be associated with autism spectrum disorders. Longer *AVPR1A* RS3 alleles were reported to be associated with greater levels of prepulse inhibition, particularly in healthy males. AVP1A mRNA levels in human hippocampus were higher in brain specimens with the long/long compared to the short/short RS3 genotype. Shorter alleles of RS1 were shown to lead to decreased transcription. Functional difference in human brain was found between subjects with short and long repeat lengths using an imaging genetics approach (5).

Maher et al. report association of *AVPR1A* 3′ UTR SNP (rs11174811) with “drug use disorder” in European American subjects (1). They also report association of this SNP with spousal relationship quality in males. This study is based on the concept of common (non drug-specific) liability and uses the candidate system of genes approach, genotyping 1536 SNPs in 106 genes. They showed impact of SNP rs11174811 on AVPR1A expression in postmortem brain samples (dorsolateral prefrontal cortex). They predicted that SNP rs11174811 disrupts a microRNA binding site; others recently demonstrated that this variant reduces microRNA-induced repression of gene expression.

We have reported an association between a different *AVPR1A* SNP (rs3759292) in the 5′ flanking region and heroin addiction in African Americans, but not Caucasians (4). The functionality of this SNP is still unknown. In contrast to this Maher et al. study (1), cases in our study were all with a specific phenotype, well-characterized severe heroin addicts in methadone maintenance treatment.

The human *AVPR1B* gene is located at chromosome 1q32. An *AVPR1B* haplotype was associated with protective effect from recurrent major depression, with mood disorders that begin in childhood and adolescence; of particular interest was the non-synonymous SNP rs35369693 (Lys65Asn), in an intracellular protein domain. A significant contribution of multiplicative effects of SNPs in *CRFRI* (SNP rs878886) and *AVPR1B* (SNP rs28632197) to panic disorder was observed in Europeans. SNP rs28632197 results in an arginine to histidine substitution in the C-terminal intracellular loop.

The Maher et al. paper extends earlier research and emphasizes the need to look at potential functioning of gene variants in the neurobiological processes of normal physiology and in addictive and other diseases (6, 7).

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