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The AVPR1A Gene and its Single Nucleotide Polymorphism rs10877969: A Literature Review of Associations with Health Conditions and Pain

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Abstract

Pain is the quintessential symptom for individuals suffering from sickle cell disease (SCD). Although the degree of suffering and the cost of treatment is staggering, SCD continues to be grossly understudied, including lack of data for pain related genes and prevalence of polymorphisms in this population. This lack of data adds to the inadequacy of pain therapy in this population. Pain genetics investigators have recently examined allele frequencies of single nucleotide polymorphisms from candidate genes in people who suffer with SCD. One of the genes identified was the arginine vasopressin receptor 1A gene (AVPR1A) and its associated single

nucleotide polymorphism (SNP) rs10877969. Progress in explaining pain related polymorphisms associated with SCD can be facilitated by understanding the literature. The purpose of this literature review was to describe mechanisms of the polymorphic gene, *AVPR1A*, and the phenotypic variations associated with its SNPs relative to health conditions and pain. Published studies were included if the research addressed AVPR1A and was a full manuscript in a peer reviewed journal, English language, a human or animal study, and published 2009 to present. Abstracts were included if they were in English and provided information not found in a full manuscript. The results of this review revealed that AVPR1A is associated with behavioral phenotypes, which include pair bonding, Autism Spectrum Disorder, musical aptitude, infidelity, altruism, monogamy, mating, substance abuse, and alcohol preference. In addition, there were associations with pain, stress pain by sex, and sickle cell pain. Summary of this literature could provide insights for future pain research of this SNP in people with SCD.

Keywords

AVPR1A; rs10877969; arginine vasopressin; polymorphism; pain; sickle cell disease; single nucleotide polymorphism

Arginine vasopressin is a 7-transmembrane domain G-protein polypeptide that has been identified as being involved in many neurological functions, including aggression, bonding, sex behavior, autism, and schizophrenia (Kreek, Zhou, & Levran, 2011). The single nucleotide polymorphism (SNP) of the arginine vasopressin receptor 1A (AVPR1A) gene (rs10877969), is one of 115 polymorphisms of 49 genes that were previously identified as a candidate pain SNP (Jhun et al., 2015). A SNP is a common type of base pair substitution, which may cause changes in protein expression that lead to differences in response to drugs, appearances, and response to environment. SNP rs10877969 is found in the promoter region of the AVPR1A gene on chromosome 12. Although this SNP has been identified as a pain related SNP, association studies need to be performed. Some investigators have reported that rs10877969 plays a role in acute, neuropathic and stress related pain (Bagdas et al., 2013; Mogil et al., 2011). In recent studies, investigators found that Catechol-O-methyltransferase (COMT), that metabolizes catecholamines, and AVPR1A are involved in pain modulation (George et al., 2015; Jhun et al., 2014). Some of the studies contained in this review, include research that was completed using animal models. These models are important because, some mechanisms are more readily accessible in animal models. Important functions of a DNA sequence tend to be highly conserved during evolution, the homolog (similar counterpart) will be recognizable in other species and in humans (ortholog) (Strachan, Goodship, & Chinnery, 2014). For genes not yet extensively studied in humans, the research in animals can be informative to guide human research.

The state of the science relative to pain management is currently being expanded, in part because of animal models. For example, animal models, were highly instrumental in recent advances in the understanding of pain mechanisms in SCD. For example, the emergence of SCD mouse models demonstrated their suitability as stable models for the study of pain in SCD, which include “knockout mouse” lines carrying exclusively human globulins after knocking out the mouse globulin gene in the Berkeley sickle cell mouse (Chang et al., 1998;

Fabry et al., 1992; Gregory et al., 2013; Nagel & Fabry, 2001; Paszty et al., 1997; Ryan, Ciavatta, & Townes, 1997; Trudel et al., 1991; Wang & Wang, 2003). The use of animal models have led to a better understanding of the types of pain commonly experienced by individuals who have SCD pain, specifically, that this population more commonly experience neuropathic pain than previously thought. From findings of the animal studies, mechanisms have been revealed and interventions have been explored (Molokie, Wang, & Wilkie, 2011; Molokie et al., 2014; Wang, Wilkie, & Molokie, 2010; Wilkie et al., 2010).

We have entered the era of personalized medicine. As a result, nurses are poised to assess, treat, and educate patients about genetically influenced components of disease (Lashley, Kasper, & Schneidereith, 2016). Genomic discoveries are rapidly advancing the science of healthcare (Hurle et al., 2013). Using skilled assessments, nurses who are knowledgeable about genetics and genomics have the ability to help individuals understand and avert potential disorders and resulting morbidity and mortality (Calzone et al., 2010).

The discovery that the SNP rs10877969 has a pain interaction associated to stress and sex, led our team to ask, “what additional findings about the function of this SNP could inform future research focused on the association of this SNP to variables important to pain of SCD?”. Specifically, a review of the AVPR1A literature can provide insights for future pain research of this gene and its associated SNP (rs10877969) in people with sickle cell disease (SCD) and other pain conditions. Patients suffering with SCD frequently report chronic, debilitating pain, yet the degree of that pain varies from patient to patient, even among individuals with the same sickle cell genotype (Adegbola, 2011). Identifying genetic polymorphisms and their influence on pain phenotypes may result in a better understanding of some of the variations seen in SCD pain (Jhun et al., 2014). Currently there is a lack of data for explaining pain related polymorphisms associated with SCD, and this significantly impedes the progress in this area of research. The purpose of this literature review was to examine the monoamine gene receptor AVPR1A and its SNP (rs10877969) to explore its mechanisms, associations with health conditions, and contributions to pain, including sickle cell pain. Explanation of genetic terms are listed in table 1.

Method

A search of PubMed, PubMed (OMIM), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Embase, and GeneCards was conducted using the following search terms: “rs10877969” and rs10877969 initially yielded three citations. Because AVPR1A, the gene of interest, is a subgroup of the vasopressin receptor family (Birnbaumer, 2000), the search was broadened using the terms “Vasopressin”, “AVPR1A”, “AVPR1A and polymorphism”, “AVPR1A and pain”, “AVPR1A and pain and polymorphism”, and “AVPR1A and sickle cell anemia or sickle cell disease” as search terms. The search from the six different databases revealed 230 published articles.

As part of the selection process, a study was included if it was a full manuscript, published in a peer reviewed journal, written in English, and reported on human or animal studies. Abstracts were included if they were in English and provided information not found in a full manuscript. The search years were limited to 2009 to present, because most SNP research

related to pain was conducted starting in 2011. Publications were excluded if they were commentaries, editorials, unpublished dissertations, primarily review articles, educational material or grey literature (scientific meetings, reports: preliminary, technical, government, or documents) (Garrard, 2011; Lang, 2010). Retrieved articles were screened based upon title and abstract, and then a second review was performed. Two hundred-thirty articles were screened by title and abstract, of those and 147 were excluded. Ancestral search, and recommendations from experts in the fields, were reviewed for further articles germane to the review topic and were not limited by years, but were limited by all the other exclusion criteria. After reviewing studies from ancestral references, and expert recommendations, 10 additional articles were acquired for eligibility determination. After further scrutiny, 50 articles were excluded for non-specificity; those articles mainly focused on AVPR1B or AVPR2A. The remaining 43 full text articles were reviewed, of which an additional 19 were excluded because they did not provide new information about AVPR1A. Twenty-four articles remained (Figure 1) for final synthesis.

Results

Sample Characteristics

The 24 retained articles were grouped into the following categories based on content: mechanisms and health problems. Mechanisms included articles exploring biochemical pathways, genomics, vasopressin, and oxytocin. The health problems were divided into three subgroups: (1) behavior/social, which included autism, bonding, stress, aggression, sex differences, and addiction; (2) pain, which included nociceptive and neuropathic; and (3) sickle cell disease (Table 2).

The AVPR1A studies included humans (adults and pediatrics) and animals (rodents), and focused on mechanisms and health problems. The range of the sample sizes for the human studies were from 33 to 1517. Ten (42%) studies included humans, nine (37%) studies included animals, three (13%) included both humans and animals, and two (8%) studies used cDNA from humans or animal. Eleven (38%) studies included mechanisms and eighteen (62%) included health problems: behavior/social ($n = 11$), pain ($n = 6$), and SCD ($n = 1$). Some of the articles included more than one subgroup. Only one citation addressed AVPR1A and SCD.

In only four human studies, investigators reported ethnicity. One research group reported studying Caucasians only whereas another group reported studying African Americans (adults) and African origin (pediatrics), a third group of researchers reported studying individuals from West Africa, and a fourth group reported studying individuals from Korea.

Mechanism

Although arginine vasopressin receptor 1A gene (AVPR1A) has three distinct receptors: AVP_{1a}, AVP_{1b}, and AVP₂; (Birnbaumer, 2000). For the purposes of this paper, our focus will be on the V_{1a} receptor. The protein name is Vasopressin V_{1a} receptor, and the gene family is arginine vasopressin and oxytocin receptors (“GeneCards,” 2009).

The human AVPR1A gene is located in the long arm of chromosome 12 (12q14.2) (Babb, Fernandez-Duque, & Schurr, 2010; Bagdas et al., 2013; Birnbaumer, 2000; Thibonnier et al., 1994; Thibonnier et al., 1996; Walum et al., 2008; Yang et al., 2010; Young, Nilsen, Waymire, MacGregor, & Insel, 1999). The protein coded from this gene behaves as a receptor for arginine vasopressin and belongs to a family of G-protein coupled receptors that include oxytocin. This family of G-coupled receptors mediates cell proliferation and contraction, platelet aggregation, glycogenolysis, and coagulation factor release (Birnbaumer, 2000; “GeneCards,” 2009). AVP_{1a} acts by binding to AVPR1A where it stimulates Gq and activates phospholipase C-beta, leading to the release of diacylglycerol and phosphatidylinositol (IP3). The latter induces the release of calcium from the endoplasmic reticulum (Yang et al., 2010). Protein kinase C is activated by diacylglycerol and calcium. The gene is conserved in the human, rhesus monkey, chimpanzee, dog, cow, chicken, rat, frog, zebrafish, and *C. elegans* (Babb et al., 2010; “GeneCards,” 2009). In some species, the 7 trans-membrane peptide hormone consisting of nine amino acids (nonapeptide) has lysine in the 8th position, but in mammals it most commonly has arginine in the 8th position, which is why it is referred to as arginine vasopressin (Birnbaumer, 2000). The human sequence is: Cys-Tyr-Phe-Gly-Asn-Cys-Pro-Arg-Gly. The receptors for AVP_{1a} are located in the kidney, liver, peripheral vasculature, and the brain (Hawtin et al., 2002).

There are several aliases for the arginine vasopressin receptor 1A: Vascular/Hepatic-Type Arginine Vasopressin Receptor, AVPR V1a, AVPR1, V1aR, V1-Vascular Vasopressin Receptor AVPR1A, SCCL Vasopressin Subtype 1a Receptor, Antidiuretic Hormone Receptor 1A, Antidiuretic Hormone Receptor 1a, V1a Vasopressin Receptor, and Vasopressin V1a Receptor (“GeneCards,” 2009). For the purposes of this paper we will use AVPR1A to discuss this gene and AVP_{1a} to discuss the receptor.

History of AVPR1A Receptor Cloning

The cloning, sequencing, and functional expression of human cDNA for AVPR1A was described in 1994 by Thibonnier and his research team. They explored structure and functional expression of AVPR1A using cDNA isolated from the liver human subjects (Thibonnier et al., 1994). In 1996, the same research team used northern blotting to show the presence of mRNA transcript (5.5kb) expressed in the liver, kidneys, heart, and skeletal muscle (Thibonnier et al., 1996). In the same year, further exploration with human genomic libraries showed AVPR1A was included in its entirety along with two coding exons (6.4kb), and PCR analysis of AVPR1A using hybrid somatic cells demonstrated localization to chromosome 12 (Thibonnier et al., 1996). The gene was physically mapped to the 12q15-q15 region via in situ hybridization (Thibonnier et al., 1996).

Results from the inositol phosphate production and calcium mobilization experiments confirm that the receptor function was preserved and coupled to phospholipase C (Koshimizu et al., 2006). Using a rat tissue of cloned rat liver cDNA that encoded the AVPR1A gene, it was observed that the amino acid identifies amongst members of the G protein-coupled superfamily and AVPR1A are congregated inside the transmembrane domains (Morel, O’Carroll, Brownstein, & Lolait, 1992). There is a 24–30% sequence

identity with the following receptors: human 5HT1a, rat substance P, rat D2 dopamine, and rat endothelin A (Morel et al., 1992).

Binding to this receptor occurs in the AVP binding site at the N terminal end of the AVPR (Hawtin et al., 2002). Researchers examined the N-terminus of V_{1a}R and analyzed individual residues that contributed to the agonist specific interaction (Hawtin et al., 2002). Evaluating the mechanisms of action, researchers found that Arg46 has a critical function for receptor activation and high affinity agonist binding (Hawtin et al., 2002). In addition, arginyl, a residue of arginine, is conserved in all neuropophysial peptide hormone receptors, and may have a crucial role in the GPCR super family for agonist:receptor interaction (Hawtin et al., 2002).

Hasan et al. (2006) explored four novel SNPs in the promoter region of AVPR1A to evaluate if they could be used as a marker for divergent platelet aggregation response to AVP. There was a significant correlation ($r = 0.59$; $p < 0.001$) between responses to AVP and those to adenosine diphosphate (ADP), but no differences in AVP – induced aggregation between subjects with and without variant alleles for the four SNPs. As a result, the four promoter region SNPs of the AVPR1A gene may not be useful as genetic markers for platelet aggregation heterogeneity (Hasan et al., 2007).

In another study, investigators explored the role of the AVPR1A in cardiovascular homeostasis using gene targeting (Koshimizu et al., 2006). There was no significant difference between the two groups for heart rate or cardiac function or heart weight. AVPR1A plays a role in normal resting arterial blood pressure regulation mainly by its regulation of circulating blood volume and baroreflex sensitivity, and mice showed altered vasopressor responses to AVP stimulation (Koshimizu et al., 2006).

AVPR1A and Oxytocin

The human AVPR1A receptor belongs to the prefamily of seven, transmembrane segment receptors with a significant sequence identity with the other members of the AVP-oxytocin family of receptors (Koshimizu et al., 2006). This receptor possesses high homology with other receptors found in the AVP and oxytocin family (Koshimizu et al., 2006). The peptides AVP and oxytocin (OT) are closely related. Vasopressin and oxytocin are nonapeptides located in the pituitary, consisting of nine amino acids arranged in a cyclic structure, and differs at only the 3 and 8 positions. Arginine and phenylalanine in vasopressin are replaced by leucine and isoleucine in oxytocin (Baribeau & Anagnostou, 2015; Ebstein et al., 2009; Jern et al., 2012; Moons, Way, & Taylor, 2014; Zietsch, Westberg, Santtila, & Jern, 2015). The structure of AVP has a strong similarity to that of oxytocin, and oxytocin appears to have an interaction with AVPR1A. Human AVP and oxytocin are located on the same chromosome, 12q14-q15, are separated by less than 15bp in most species, both neuropeptides are synthesized in the hypothalamus and secreted from the posterior pituitary gland into the bloodstream (Birnbaumer, 2000; Gonzalez-Hernandez, Rojas-Piloni, & Condes-Lara, 2014; Juif & Poisbeau, 2013). AVP's two primary functions are: water and salt retention and vasoconstriction, other functions include cell proliferation, platelet aggregation, release of factor VIII, von Willebrand factor, social recognition, and circadian tau (Birnbaumer, 2000; Koshimizu et al., 2006; Koshimizu & Tsujimoto, 2009; Kreek et al.,

2011; Moons et al., 2014), whereas the major role of oxytocin, is to regulate parturition, lactation, and bonding behavior (Schaschl et al., 2015).

Behavioral Phenotypes

AVP plays a role in social behavior, jet-lag, sexual motivation, and maternal bonding (close relationship to oxytocin) (Hammock & Young, 2005; Lim et al., 2004; Maher, 2011; Meyer-Lindenberg et al., 2009; Mogil et al., 2011; Walum et al., 2008; Yamaguchi et al., 2013; Young et al., 1999). Researchers examined transgenic mice that had neuroanatomical patterns of AVP_{1a} receptors in the brain similar to prairie voles, a species used widely as an animal model in pair-bonding research, and reported that gene expression for receptor AVPR1A may have functional association to species-typical behaviors in males (Young et al., 1999). Young et al. (2003) later went on to report that prairie voles and montane voles had species-specific behavior patterns associated with differences in a microsatellite in the 5' regulatory region that encodes AVPR1A (Hammock & Young, 2005), where selective blocking of AVPR1A in the ventral pallidum, a reward circuit pathway, decreased pair bonding in prairie voles, therefore AVPR1A is critical for pair bonding (Hammock & Young, 2005). While studying double knockout mice that lacked receptors for both AVP_{1a} and AVP_{1b}, it was found that these mice were resistant to jet-lag, suggesting that vasopressin signaling may also be a target for managing circadian misalignment (Yamaguchi et al., 2013).

Studies, in both humans and animals, on the roles of oxytocin and arginine vasopressin (AVPR1A) have shown they play a role in social processes in mammals for social deficits and neurodevelopmental disorders including autism spectrum disorder, and ejaculatory function (Baribeau & Anagnostou, 2015; Jern et al., 2012; Lim et al., 2004).

The 5' flanking region of AVPR1A contains three polymorphic microsatellite repeats ([GT]₂₅, RS1, and RS3): where activation stimulates phospholipase C. Differing lengths of these repeats have been described in various studies and are associated with behavioral traits, thereby suggesting that they are relevant for brain function related to emotional arousal and social behavior. Subjects with shorter RS3 (repeat sequence microsatellite) 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 elevated levels of prepulse inhibition (the weaker prestimulus inhibits reaction to a subsequent stronger stimulus), particularly in healthy males (Kreek et al., 2011). This AVPR1A association with the well-known neurobiological phenomenon of prepulse inhibition suggests that a weak startling sound or non-noxious tactile stimuli in those with longer AVPR1A RS3 alleles could blunt future reactions to strong startling stimuli and this decreased startle effect may differ by sex (Kreek et al., 2011).

Yang et.al investigated the association of Korean Autism Spectrum disorder (ASD) families with three AVPR1A SNPs. They demonstrated a possible association between the SNPs and the phenotype of ASD. The findings were statistically significant for association between autism and SNPs in the promoter region of chromosome 12 (Yang et al., 2010).

Pain

Vasopressin has been described as playing a crucial role in the modulation of pain and several studies have shown that AVP can regulate the pain process in the brain through the mediation of central cholinergic and opioidergic systems (Bagdas et al., 2013; Mogil et al., 2011). In a recent study, a three-way interaction between, genetics (AVPR1A, rs10877969), sex, and acute stress in both mice and humans was demonstrated. In male volunteers reporting stress at the time of testing (capsaicin pain) that differed based on genotype, and no effects of stress on genotype were found in women (Mogil et al., 2011). Allele frequencies of rs10877969 differed in White and Asian versus African American volunteers, and the lower pain rating of male volunteers was not observed in African Americans (Mogil et al., 2011). The involvement of AVPR1A in capsaicin pain indicates that vasopressin may have analgesic properties against this pain modality (Mogil et al., 2011). The mouse AVPR1A gene, encoding for AVP_{1a}, translates to humans in its role in pain and genotype interacts with sex and acute stress (Mogil et al., 2011). Further examination of the model revealed an endogenous pain relief pathway induced by stress and mediated by AVPR1A, which was replicated cross species (between mouse and human) in a three-way interaction among genotype, stress level, and sex (Wiltshire, Maixner, & Diatchenko, 2011).

Another genetic association model was used to observe physical impairment and acute pain. Parr, Fillingim, Wallace, et al (2012) examined AVPR1A and SNP rs10877969 along with SNPs of other genes and described it as having an impact on physical impairment and range of motion. Flexion and range of motion deficit was associated with AVPR1A and COMT, while internal rotation deficit and abduction deficit was associated with AVPR1A. Physical impairment in range of motion and strength had a stronger association with variation in inflammatory and pain modulating genes in comparison to psychological factors in which all predictors had *p*-values of less than .05 (Parr et al., 2012). It was later reported that, after muscle injury, neuronal excitability and vasopressin-mediated endogenous analgesia may affect the pain-related influence of emotional or cognitive states (George et al., 2014). The interaction between pain catastrophizing and depression revealed the phenotype for shoulder pain duration. SNPs from the gene AVPR1A were determined to be possible predictors for shoulder pain duration. Future investigations may explore similar interactions to determine the clinical applicability for the prediction of treatment outcomes.

Studies indicate that both OT and AVP play a role in the inhibition of nociception, but the identity of the main receptor remains obscure. Peng, Qu, Qiu, et al (2015), demonstrated the antinociceptive effect of formalin induced spontaneous nociception. In this study, they showed that spinal AVP reduced pain responses when mice were injected with 5% formalin, which induced spontaneous nociceptive behavior (licking and lifting of the injection site). Spinal dose reduced formalin-induced spontaneous nociception in wild-type mice, and had no effect on mice that had been genetically modified (AVP_{1a} receptor knock-out, Peng, 2015).

Oxytocin has been shown to mediate pain by blocking the activity of blocking A delta and C fibers, and by activating various pathways in the neuronal system. Studies that explore analgesia at the periphery have indicated oxytocin receptor (OTR) involvement whereas

others have shown AVPR1A involvement (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012; Gonzalez-Hernandez et al., 2014).

Using Cytidine-5'-diphosphate-choline (CDP-Choline; citicoline) in the rat model, Bagdas et al. (2013), examined analgesic responses via CDP-choline. CDP-Choline enhances central and peripheral vasopressin levels in acute, inflammatory and chronic injury-induced neuropathic pain models in rats without any motor impairment (Bagdas et al., 2013). Centrally administered CDP-choline elicited an analgesic effect through central cholinergic and opioidergic systems, and demonstrates evidence for the utility of centrally acting cholinergic and vasopressinergic agonists in the management of acute and neuropathic pain (Bagdas et al., 2013; Ballas, Gupta, & Adams-Graves, 2012).

Sickle Cell Disease

Recently published, (Jhun et al., 2015) reported on patients with SCD from two institutions who participated in a pain study exploring pain phenotypes. The population consisted of African American adults and pediatrics patients of African origin. (Jhun et al., 2015) explored 115 pain related SNPs in 49 candidate genes and compared them to current literature. The genes and related SNPs, are thought to be a part of the monoamine neurotransmitter system and have been previously implicated in pain. The AVPR1A gene and a related SNP (rs10877969) were identified in this study as prospective candidate for pain genetics studies (Jhun et al., 2015).

Discussion

The purpose of this literature review on the polymorphisms of AVPR1A was to examine its mechanisms and associated health conditions, including SCD. This review indicates that studies on pain-related SNPs are limited in number, and studies on pain related SNPs in the sickle cell population are even more limited. In a recent study, this SNP, rs10877969, was found to have a possible role for differences in the perception of pain.

In the mechanisms section, we explored current research on the function of this receptor, and current mechanisms for cloning and genotyping. AVPR1A was found to be highly linked with the oxytocin receptor (Baribeau & Anagnostou, 2015; Birnbaumer, 2000; Gonzalez-Hernandez et al., 2014; Jern et al., 2012; Juif & Poisbeau, 2013; Moons, Baldwin, Taylor, 2014), which explains some of the overlap in functions.

AVPR1A binding has been shown to be highly linked to behaviors and behavioral health conditions. The most prevalent health condition associated with behavior was Autism Spectrum Disorder (ASD) (Baribeau & Anagnostou, 2015; Meyer-Lindenberg et al., 2009; Yang et al., 2010). Associated with features seen in ASD, AVPR1A was seen to be linked to associated behaviors such as bonding, stress, and addiction (hyper fixation) (Baribeau & Anagnostou, 2015; Hammock & Young, 2005; Lutz, Meiler, Bekker, & Tao, 2015; Maher, 2011; Moons, Baldwin, Taylor, 2014; Ukkola-Vuoti et al., 2011; Walum et al., 2008; Yang et al., 2010). In a recent study exploring genetic factors and physical impairment, it was shown that AVPR1A has a role in pain modulation for acute shoulder pain (George et al., 2014). More recently, a three-way interaction was demonstrated between sex, environment, and

stress. This interaction was shown in both the animal and human models (Mogil et al., 2011; Wiltshire et al., 2011)

Although the findings regarding AVPR1A and SCD are limited to only one publication, the findings from another study suggested a link to SCD pain for newly explored pain SNPs (Jhun et al., 2015). Jhun and colleagues (Jhun et al., 2014) found that DRD3 Ser9Gly and COMT Val158Met may contribute to pain heterogeneity in SCD. They also found that patients were likely to have a higher acute care utilization for acute pain if they had the COMT 158 Met allele or Met/Met genotype. Similar clinical SCD investigations are warranted for AVPR1A.

This review explored the AVPR1A SNP and associated health problems (social/behavioral, pain, and sickle cell disease). Limitations of this review include the recognition that SCD is understudied and additional studies need to be done to explore polymorphisms related to pain that could result in more desirable patient outcomes with respect to pain. Other studies, such as those reported in languages other than English may provide additional insight into the function of AVPR1A.

In summary, future pain related SCD research should include exploring rs10877969 using sufficiently sized samples, and further exploring differences between genotypes in African Americans compared to individuals of African origin. In addition, studies are warranted to explore AVPR1A for associations with acute or chronic pain of SCD and if stress or sex are associated with AVPR1A and clinical SCD pain. Information gained from this review will serve to increase understanding of the contributions that genetics and genomics play in health science to aid in health promotion and disease prevention, inform policymaking groups, and guide future research that further generates new knowledge for clinical practice and is focused on improving safe and effective pain management (Calzone et al., 2010).

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Figure 1.
Search strategy

Table 1.

Glossary of Genetic Terms

Term	Definition
5' flanking region	The end of the DNA strand that is linked by a 3' carbon sugar (Strachan, Goodship, & Chinnery, 2014).
Allele	"Any one of two or more alternate forms of a gene located at the same locus" (Lashley, Kasper, & Schneidereith, 2016), pg. 489, e.g., one of G, A, T, C.
Conserve sequence	DNA sequence that is highly similar or identical across organisms; suggests an important function (Strachan et al., 2014).
G Protein	Guanine nucleotide-binding proteins, or G proteins, act as molecular switches inside cells to transmit signals from a variety of stimuli outside a cell to its interior and play important roles in pain modulation (Ahmad & Dray, 2004).
Gene	A functional DNA unit of heredity that is used to make a product, such as a protein (Strachan et al., 2014).
Homolog	Sequences of two or more genes that are highly similar due to a strong evolutionary relationship (Strachan et al., 2014).
Knockout gene	The targeted creation of a null allele by within a predetermined gene (Strachan et al., 2014).
Ortholog	Equivalent genes present in two or more species that evolved from a common evolutionary ancestor (Strachan et al., 2014).
Phenotype	"A physical appearance resulting from the interaction between genes and the environment" (Lashley et al., 2016), pg. 498.
Polymorphism	DNA variants at a significant frequency in the population (Strachan et al., 2014).
Precision Medicine	An approach to the treatment and prevention of disease that considers the individual variability of environment, genes, and lifestyle of each individual (Filipski, 2016, June 28).
Promoter region	A region of DNA that initiates transcription of a gene (Strachan et al., 2014).
Sequence Identity	The number of nucleotides that are matched exactly between two different sequences (Rameez, 2017, April 24).
Single Nucleotide Polymorphism (SNP)	A type of variation in a single base pair of the DNA at specific location in the genome (Lashley et al., 2016).
Transgenic mice	Artificially introduced DNA becomes incorporated into the germ line (Strachan et al., 2014).

Table 2

Summary of the Findings

Author Year	Study Purpose	Sample Description	Key Concept(s) & Major Findings	Conclusions Study Limitations
Morel et al., 1992	Examine cloned cDNA encoding hepatic AVPR1A.	Animals (Rats)	<i>Mechanisms.</i> Cloned cDNA encodes hepatic AVPR1A. The hepatic cDNA encodes the seven transmembrane domains and binds AVPR1A. The binding affinities of the cloned cDNA is similar to those of the native rat AVPR1A DNA. The corresponding mRNA is dispersed in the rate tissues where AVPR1A are known to be located.	Amino acid identities amongst members of the G protein-coupled superfamily and AVPR1A are congregated inside the transmembrane domains. There is a 24–30% sequence identity with the following receptors: human 5HT1a, rat substance P, rat D2 dopamine, and rat endothelin A.
Thibonnier, M., 1994	Describe the cloning, sequencing and functional expression of cDNA AVPR1A.	Human Animal	<i>Mechanisms.</i> The structure and functional expression of human AVPR1A cDNA isolated from the liver.	Human AVPR1A receptor belongs to the prefamily of seven-transmembrane segment receptors with a significant sequence identity with the other members of the AVP-oxytocin family of receptors.
Thibonnier, M., 1996	Describe genomic characteristics, tissue expression, chromosomal localization, and regional mapping of the human AVPR1A gene.	Human	<i>Mechanisms.</i> Exploration of northern blotting showed presence of mRNA transcript (5.5kb), expressed in the liver, kidneys, heart, and skeletal muscle. Exploration with human genomic libraries showed AVPR1a is included in its entirety and includes two coding exons (6.4kb). When analyzing AVPR1A by PCR using hybrid somatic cells, localization to chromosome 12 was revealed, and use of in situ hybridization demonstrated that the gene was physically mapped to the 12q15-q15 region.	AVPR1A was physically mapped to chromosome 12, region12q14-q15.
Young, L., 1999	Behavior response differences in the prairie vole verses the montane vole are related to AVPR1A receptor binding pattern differences between the species.	Animal (mice)	<i>Behavior.</i> Transgenic mice that have neuroanatomical patterns of AVPR1A receptors in the brain similar to prairie voles. Gene expression for receptor AVPR1A located in the brain, may have a functional association to special typical behaviors in males.	Arginine vasopressin administered centrally, increases affiliative behavior in the male monogamous prairie vole and not the promiscuous male montane vole.
Birnbaumer, M. 2000	Explore the biological effects of AVPR1A.	cDNA isolation (tissue variability)	<i>Mechanisms.</i> Comparison of the structure of the three receptor subsites of AVP: structure, signaling, and testing. Comparison of AVR to OTR.	Maintenance of water homeostasis is the most important physiological role of vasopressin

Author Year	Study Purpose	Sample Description	Key Concept(s) & Major Findings	Conclusions Study Limitations
Hawtin, S. R., 2002	Explore the V _{1a} R N-terminus and analyze individual residues that contribute to the agonist specific interaction, evaluate the required side-chain properties and suggest a mechanism of action.	Cell culture (HEK 293T cells)	<i>Mechanisms.</i> Arg ⁴⁶ had a decreased affinity for AVP leading to a 1300-fold increase with K _d , to the wild-type, but not with any class of antagonist. N-terminus agonist recognition site was restricted to six residues (Leu ⁴² , Gly ⁴³ , Asp ⁴⁴ , Val ⁴⁵ , Arg ⁴⁶ , Asn ⁴⁷). Constructs without Arg ⁴⁶ had impaired intracellular signaling.	Arg46 has a critical function for receptor activation and high affinity agonist binding. Arginly is conserved in all neurohypophysial peptide hormone receptors, and may have a crucial role in the super family of GPCRs for interaction of agonist:receptor. May play a role in substance P binding.
Lim, M. 2004	Demonstrate the role of AVPR1A expression in social bonding.	Animals (voles)	<i>Behavior.</i> AVPR1A is expressed in a higher concentration in monogamous, prairie voles than found in promiscuous, meadow voles. Partner preference on meadow voles was increased when exposed to AVPR1A gene (via gene transfer) in the ventral forebrain.	Similar polymorphisms in the AVPR1A promoter region humans has been linked to autism. Human AVPR1A polymorphisms may contribute to human variability in social behavior.
Hammock, E. 2005	To determine whether or not intraspecific variation in the microsatellite is sufficient to change gene expression.	Animals (prairie voles)	<i>Behavior.</i> There are significant genotype differences in the frequency of pup licking and grooming. In partner preference, long and short allele spent equal amounts of time in total social contact and long allele males spent more time with their partner compared with the stranger in long allele males, and in short allele males. Long allele-males displayed partner preference, whereas short-allele animals did not.	Species specific patterns of AVPR1A expression appear to be regulated by differences in a microsatellite in the 5' regulatory region of the gene encoding AVPR1A. Vasopressin systems contribute to male, not female, species-typical behaviors.
Koshimizu, T. 2006	Explore the role of the AVPR1A in cardiovascular homeostasis using gene targeting.	Animals (mice)	<i>Mechanisms.</i> No significant difference between the two groups for HR or cardiac function. No difference in heart weight. Mice showed altered pressor responses to AVP stimulation.	AVPR1a plays a role in normal resting arterial BP regulation mainly by its regulation of circulating blood volume and baroreflex sensitivity.
Hasan, K 2007	Evaluate four SNPs in the promoter region of AVPR1A to evaluate if they could be used as a marker for divergent platelet aggregation response to AVP.	n = 33 Human (Adult)	<i>Mechanisms.</i> Significant correlation ($r = 0.59$; $P < 0.001$) between responses to AVP and those to ADP. No differences in AVP – induced aggregation between subjects with and without variant alleles for the four SNPs.	Four promoter region SNPs of the AVPR1A gene may not be useful as genetic markers for platelet aggregation heterogeneity. Platelet aggregation varies among individuals.

Author Year	Study Purpose	Sample Description	Key Concept(s) & Major Findings	Conclusions Study Limitations
Walum, H., 2008	Investigate if the variability in the 5' flanking regions of AVPR1A affects pair-bonding behavior in prairie voles.	Human model n = 552 Adults Twin pairs Spouses and offspring; Animals (Prairie voles)	<i>Behavior.</i> Men that were homozygous for the 334 allele were more likely to be unmarried than the other men.	Results suggest an association between single gene and pair-bonding behaviors in humans, and indicate a well characterized influence of AVP on pair-bonding in voles may be of relevance to humans.
Meyer-Lindenberg, A. 2009	Explore differences in amygdala activation related to specific alleles.	Humans (Adults) n = 258	<i>Behavior.</i> Significant association in AVPR1A with human personality traits. Alleles for polymorphic microsatellite repeats linked to autism are associated with differential amygdala activation and personality traits in humans.	Human amygdala function is strongly associated with genetic variation in AVPR1A.
Yang, S. 2010	Determine the association between arginine vasopressin receptor 1A gene (AVPR1A) and autism spectrum disorder (ASD).	Humans n = 151 trios (triplet sets)	<i>Behavior.</i> Significant association between autism and SNPs (rs7294536, rs10877969, and between autism and haplotype model. ADR-I scores for failure to develop peer relationships were higher in individuals with the AA genotype than in subjects with the AG genotype.	Possible association between the two SNPs and ASDs.
Maher, B.S., 2011	Explore association between AVPR1A and drug use disorders (DUD)	Human (Adults) n = 757	<i>Behavior.</i> Associations to DUD were detected in three SNPs in AVPR1A.	AVPR1A may influence the risk of dysregulated behavioral outcomes through social/affiliative behaviors.
Mogil, J. 2011	Explore the effects of Avpr1a pain and analgesic responses in humans and rodents.	Humans (Adults) n = 104 Animals (Mice)	<i>Pain.</i> No genetic association with either SNP was seen in overall mean pain ratings.	Role of AVPR1A in pain is specific to the chemical/inflammation modality, most chronic pain states feature inflammation, and the capsaicin test is thought to be an excellent model of human clinical pain.
Ukkola-Vuoti, L., 2011	Investigate the role of AVPR1A, serotonin, and dopamine systems in active and passive listening to music in families tested for music aptitude.	Human (Adults and Pediatrics) n = 437 Age = 8–93 years	<i>Behavior.</i> Genetic association between amounts of active and passive current and lifelong listening to music. Association with the AVPR1A receptor gene that mediates the effects of highly conserved AVP suggests that listening to music is related to the pathways affecting attachment behavior and social communication.	Willingness to listen to music is related to neurobiological pathways affecting social affiliation and communication. Similarities between human and animal song have been detected.
Jern, P. 2012	Investigate associations between SNPs linked to OT and AVP receptor genes and	Human (Adult) n = 1517 twin males	<i>Behavior.</i> Heterozygote effect on one SNP in the OTR gene (rs75775), individuals had a significantly elevated risk for symptoms of premature ejaculation.	Rare variants in AVP genes may have significant effects on premature ejaculation.

Author Year	Study Purpose	Sample Description	Key Concept(s) & Major Findings	Conclusions Study Limitations
	ejaculatory function.			
Bagdas, D. 2013	Assess possible role of AVP receptors in the analgesic effect of CDP-choline on acute and neuropathic pain in rats.	Animals (rats)	<i>Pain.</i> Intracerebroventricular administration of CDP-choline increased plasma vasopressin levels in a dose-dependent and time-dependent manner. Intracellular administration of CSP-choline increases Ach levels in the caudate nucleus and periaqueductal gray.	*Intracerebroventricular administration of CDP-choline elicits an analgesic effect in rat models of acute and neuropathic pain. Central AVP ₁ and AVP ₂ are involved in the analgesic effect of CDP-choline. Histological studies suggest that AVP-containing fibers may play a role in the pain modulating nuclei of the brain.
Juif, P. 2013	Characterize the effects of physiological blood concentrations of OT and AVP on spinal nociception and on pain responses.	Animals (Rats)	<i>Pain.</i> Action potentials mediated by C-type nociceptive fibers was strongly reduced (antinociception) after IV injections of low doses of OT (<5 µg) or AVP (<500 pg). An increase (pronociception) was observed at higher doses.	Blood levels of OT and AVP modulate nociception, windup plasticity and pain responses. These effects remain to be identified but are likely to be C-type nociceptors
Yamaguchi, Y., 2103	Identify candidate signaling molecules that might contribute to jet-lag.	Animal model (mice)	<i>Behavior.</i> V1a and V1b receptor double knockout mice in a light controlled environment.	Mice without arginine vasopressin 1a and 1b receptors were resistant to jet-lag. Results suggest that vasopressin signaling may be a target for managing circadian misalignment.
George, S., 2014	Identify genetic and psychological interactions predictive of exercise-induced shoulder pain phenotypes.	Human	<i>Pain.</i> After muscle injury, neuronal excitability and vasopressin-mediated endogenous analgesia may affect the pain-related influence of emotional or cognitive states. The interaction between pain catastrophizing and depression revealed the phenotype for shoulder pain duration.	SNPS from the gene AVPR1A were determined to be possible predictors for shoulder pain duration. Future investigations may explore similar interactions to determine the clinical applicability for the prediction of treatment outcomes.
Moons, W., 2014	Assess the baseline and post stressor levels of plasma OT, plasma AVP and its effect on positive affect, and anger.	Human (Adults) n = 166 (68 men/98 women)	<i>Behavior.</i> Women with high levels of post stressor OT and the GG genotype felt the most positive affect after the stressor. Men with high levels of post stressor AVP polymorphism reported more post stressor anger than non-carriers.	Oxytocin and vasopressin receptor genes interact with levels of OT and AVP to predict sex-specific emotional response to stress. Biological sex, receptor polymorphisms, and endogenous neuropeptide levels jointly predict emotional outcomes in humans.
Jhun, E. H., et.al.; 2015	Identify genetic polymorphisms and their influence on pain phenotypes to explain pain variances seen in SCD.	Humans (Adult and pediatric) African origin African American n = 199	<i>Pain.</i> Genotype and allele frequencies of SNPs were found to be different between AA cohort and West A cohort; or adult and pediatric cohort. Candidate pain genetic studies may aid in designing precision pain medication. Sickle Cell Disease	Differences were found between the two cohorts, but it is unclear as to whether the difference was attributed to being African vs African American, or pediatric vs adult. Relation to monoamine neurotransmitter and TNP (Transient Receptor Potential Channels) and its implication to pain for targeted therapies.

Author Year	Study Purpose	Sample Description	Key Concept(s) & Major Findings	Conclusions Study Limitations
Peng, F, 2015	Explore the role of spinal vasopressin and its impact on GABA _A receptor function in mice.	Animals (Mice)	<i>Pain.</i> Spinal AVP dose dependent reduced formalin-induced spontaneous nociception in wild-type mice. AVP had no effect on formalin-induced spontaneous nociception in AVPR1A receptor in knock-out (V _{1A} ^{-/-}) mice. Antinociceptive effect of AVP was reversed by co-treated GABA _A receptor against. AVP potentiated GABA-activated currents in wild-type littermates, but not V _{1A} ^{-/-} mice.	Spinal AVP can exert an antinociceptive effect on the second phase of formalin-induced spontaneous nociception. A novel mechanism of AVP analgesia by enhancing GABA _A receptor function in primary sensory neurons via AVPR1A receptors.

Articles are listed chronologically because some of the articles include information relevant to more than one category.