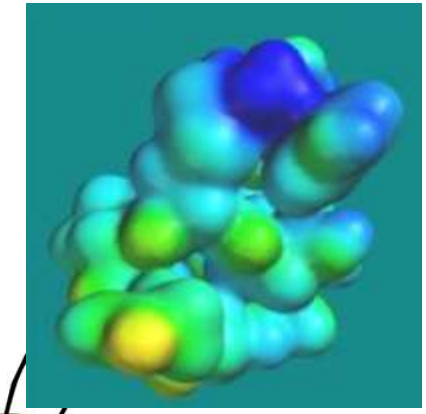
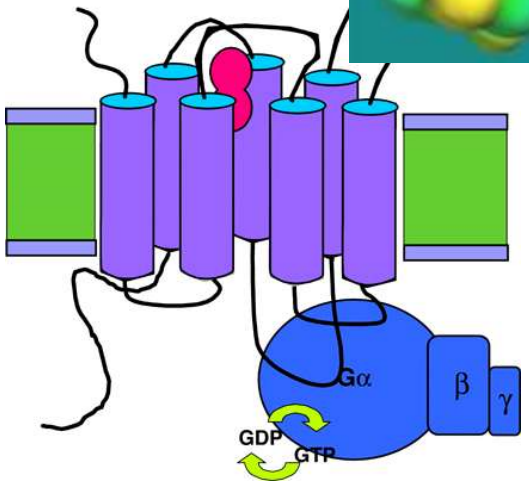
VASOPRESSIN:

from VNTRs to cellular mechanisms to emotion… the fraught nonapeptide





Arginine Vasopressin and Oxytocin Modulate Human Social Behavior

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Increasing evidence suggests that two nonapeptides, arginine vasopressin and oxytocin, shape human social behavior in both nonclinical and clinical subjects. Evidence is discussed that in autism spectrum disorders genetic polymorphisms in the vasopressin–oxytocin pathway, notably the arginine vasopressin receptor 1a (AVPR1a), the oxytocin receptor (OXTR), neurophysin I and II, and CD38 (recently shown to be critical for social behavior by mediating oxytocin secretion) contribute to deficits in socialization skills in this group of patients. We also present first evidence that CD38 expression in lymphoblastoid cells derived from subjects diagnosed with autism is correlated with social skill phenotype inventoried by the Vineland Adaptive Behavioral Scales. Additionally, we discuss molecular genetic evidence that in nonclinical subjects both AVPR1a and OXTR genes contribute to prosocial or altruistic behavior inventoried by two experimental paradigms, the dictator game and social values orientation. The role of the AVPR1a is also analyzed in prepulse inhibition. Prepulse inhibition of the startle response to auditory stimuli is a largely autonomic response that resonates with social cognition in both animal models and humans. First results are presented showing that intranasal administration of arginine vasopressin increases salivary cortisol levels in the Trier Social Stress test. To summarize, accumulating studies employing a broad array of cutting-edge tools in psychology, neuroeconomics, molecular genetics, pharmacology, electrophysiology, and brain imaging are beginning to elaborate the intriguing role of oxytocin and arginine vasopressin in human social behavior. We expect that future studies will continue this advance and deepen our understanding of these complex events.

Neuron. 2010 Mar 25;65(6):831-44.

Genetics of human social behavior.

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Abstract

Human beings are an incredibly social species and along with eusocial insects engage in the largest cooperative living groups in the planet's history. Twin and family studies suggest that uniquely human characteristics such as empathy, altruism, sense of equity, love, trust, music, economic behavior, and even politics are partially hardwired. The leap from twin studies to identifying specific genes engaging the social brain has occurred in the past decade, aided by deep insights accumulated about social behavior in lower mammals. Remarkably, genes such as the arginine vasopressin receptor and the oxytocin receptor contribute to social behavior in a broad range of species from voles to man. Other polymorphic genes constituting the "usual suspects"--i.e., those encoding for dopamine reward pathways, serotonergic emotional regulation, or sex hormones--further enable elaborate social behaviors.

Prog Brain Res. 2008;170:435-49.

Molecular genetic studies of the arginine vasopressin 1a receptor (AVPR1a) and the oxytocin receptor (OXTR) in human behaviour: from autism to altruism with some notes in between.

Israel S, Lerer E, Shalev I, Uzefovsky F, Reibold M, Bachner-Melman R, Granot R, Bornstein G, Knafo A, Yirmiya N, Ebstein RP.

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Abstract

Converging evidence from both human and animal studies has highlighted the pervasive role of two neuropeptides, oxytocin (OXT) and arginine vasopressin (AVP), in mammalian social behaviours. Recent molecular genetic studies of the human arginine vasopressin 1a (AVPR1a) and oxytocin (OXTR) receptors have strengthened the evidence regarding the role of these two neuropeptides in a range of normal and pathological behaviours. Significant association between both AVPR1a repeat regions and OXTR single nucleotide polymorphisms (SNPs) with risk for autism has been provisionally shown which was mediated by socialization skills in our study. AVPR1a has also been linked to eating behaviour in both clinical and non-clinical groups, perhaps reflecting the social and ritualistic side of eating behaviour. Evidence also suggests that repeat variations in AVPR1a are associated with two other social domains in Homo sapiens: music and altruism. AVPR1a was associated with dance and musical cognition which we theorize as reflecting the ancient role of this hormone in social interactions executed by vocalization, ritual movement and dyadic (mother-offspring) and group communication. Finally, we have shown that individual differences in allocation of funds in the dictator game, a laboratory game of pure altruism, is predicted by length of the AVPR1a RS3 promoter-region repeat echoing the mechanism of this hormone's action in the vole model of affiliative behaviours and facilitation of positive group interactions. While still in its infancy, the current outlook for molecular genetic investigations of AVP-OXT continues to be fascinating. Future studies should profitably focus on pharmacogenomic and genomic imaging strategies facilitated by the ease and efficacy of manipulating AVP-OXT neurotransmission by intranasal administration. Importantly, physiological measures, behavioural paradigms and brain activation can be informed by considering between-group and also within-group individual differences defined by common polymorphisms. Ultimately, investigators should strive to develop a cohesive model explaining how genomic variations are translated into individual and group differences in higher-order social behaviours.

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AVPR1a and *SLC6A4* Gene Polymorphisms Are Associated with Creative Dance Performance

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Dancing, which is integrally related to music, likely has its origins close to the birth of *Homo sapiens,* and throughout our history, dancing has been universally practiced in all societies. We hypothesized that there are differences among individuals in aptitude, propensity, and need for dancing that may partially be based on differences in common genetic polymorphisms. Identifying such differences may lead to an understanding of the neurobiological basis of one of mankind's most universal and appealing behavioral traits—dancing. In the current study, 85 current performing dancers and their parents were genotyped for the serotonin transporter (*SLC6A4:* promoter region HTTLPR and intron 2 VNTR) and the arginine vasopressin receptor 1a *(AVPR1a:* promoter microsatellites *RS1* and *RS3).* We also genotyped 91 competitive athletes and a group of nondancers/nonathletes ($n = 872$ subjects from 414 families). Dancers scored higher on the Tellegen Absorption Scale, a questionnaire that correlates positively with spirituality and altered states of consciousness, as well as the Reward Dependence factor in Cloninger's Tridimensional Personality Questionnaire, a measure of need for social contact and openness to communication. Highly significant differences in *AVPR1a* haplotype frequencies *(RS1* and *RS3),* especially when conditional on both *SLC6A4* polymorphisms (HTTLPR and VNTR), were observed between dancers and athletes using the UNPHASED program package (Cocaphase: likelihood ratio test [LRS] = 89.23, $p = 0.000044$). Similar results were obtained when dancers were compared to nondancers/nonathletes (Cocaphase: LRS = 92.76, $p = 0.000024$). These results were confirmed using a robust family-based test (Tdtphase: LRS = 46.64, $p = 0.010$). Association was also observed between Tellegen Absorption Scale scores and *AVPR1a* (Qtdtphase: global chi-square = 26.53, $p = 0.047$), *SLC6A4* haplotypes (Qtdtphase: chi-square = 2.363, $p = 0.018$), and *AVPR1a* conditional on *SCL6A4* (Tdtphase: LRS = 250.44, $p = 0.011$). Similarly, significant association was observed between Tridimensional Personality Questionnaire Reward Dependence scores and *AVPR1a RS1* (chi-square = 20.16, $p = 0.01$). Two-locus analysis (*RS1* and *RS3* conditional on HTTLPR and VNTR) was highly significant (LRS = 162.95, $p = 0.001$). Promoter repeat regions in the *AVPR1a* gene have been robustly demonstrated to play a role in molding a range of social behaviors in many vertebrates and, more recently, in humans. Additionally, serotonergic neurotransmission in some human studies appears to mediate human religious and spiritual experiences. We therefore hypothesize that the association between *AVPR1a* and *SLC6A4* reflects the social communication, courtship, and spiritual facets of the dancing phenotype rather than other aspects of this complex phenotype, such as sensorimotor integration.

"We first examined the arginine vasopressin 1a receptor (AVPR1a) promoter region microsatellites (allele frequencies for RS1 and RS3) and the serotonin transporter gene (SLC6A4)… to compare allele and haplotype frequencies between two groups, dancers versus athletes. … Single-locus analysis showed significance for the RS3 marker and a two-locus haplotype (RS1 and RS3). When the AVPR1a polymorphisms were analyzed conditional on the SLC6A4 polymorphisms, highly significant differences in allele and haplotype frequencies were observed.

microsatellite promoter-region instability may be a major factor producing diversity in both region-specific gene expression and the resulting phenotypes

association between AVPR1a and dancing may be reflecting the importance of social relations and communication in the dance form and that both dance and its associated gene, AVPR1a, contribute to molding social interactions from the molecular level to the dance floor."

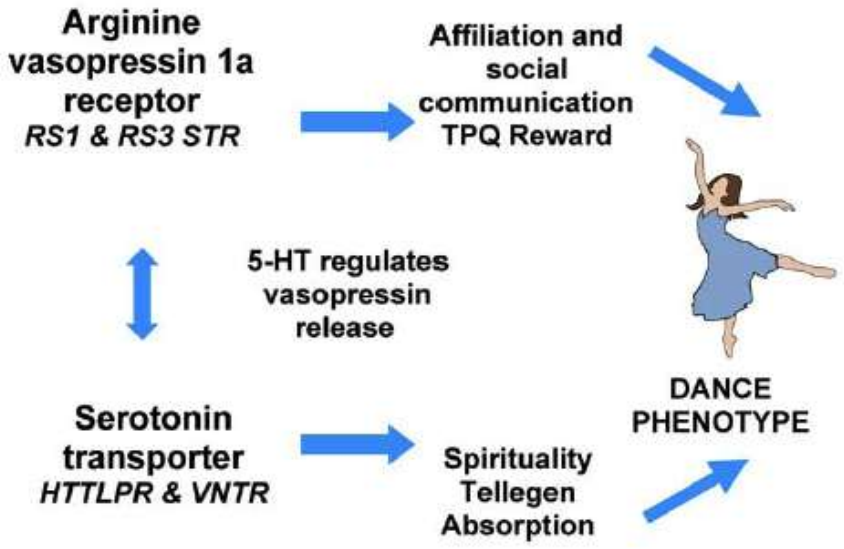
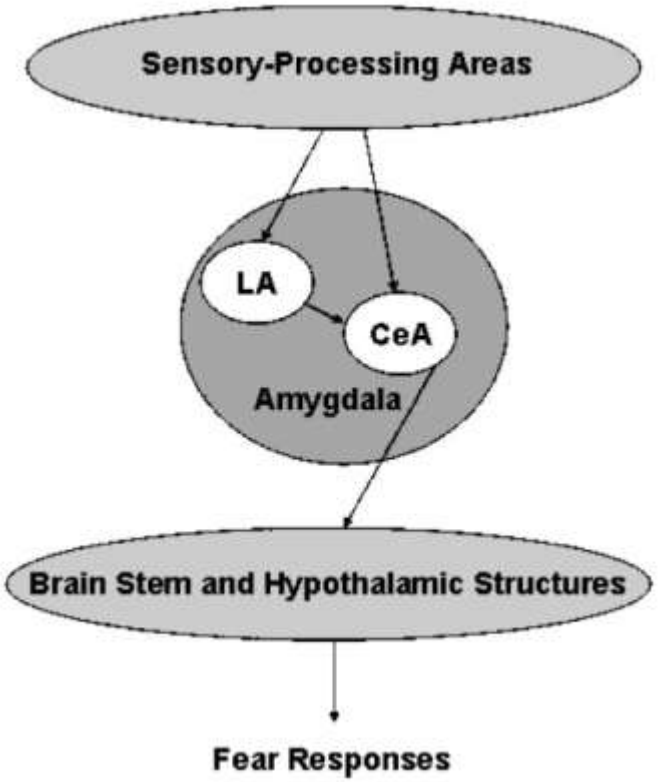
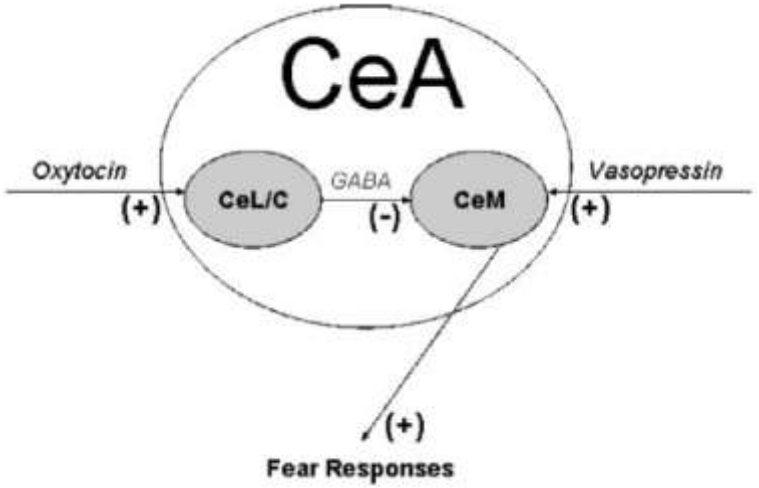


Figure 3. Epistatic Interaction between *AVPR1a* and *SLC6A4* Contributes to the Creative Dance Phenotype





Peptides of love and fear: vasopressin and oxytocin modulate the integration of information in the amygdala

Jacek Dębiec

BioEssays 27:869–873, © 2005 Wiley Periodicals, Inc.

What level of analysis do these figures show? What levels were covered in the paper?

DIRECT EVIDENCE THAT AVP ACTIVATES STRESS PHYSIOLOGY

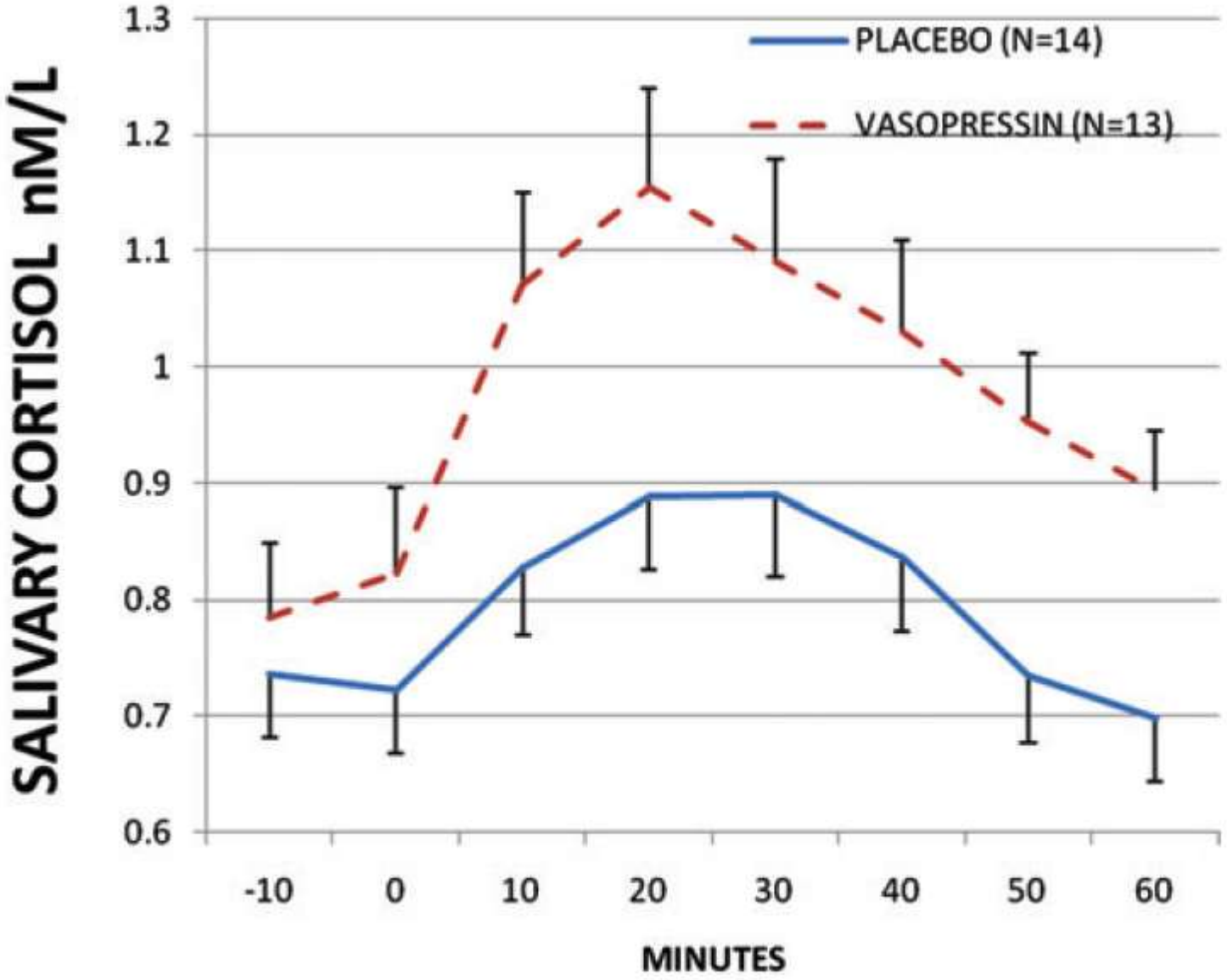


Figure 5. The effect of arginine vasopressin (AVP) administered intranasally on salivary cortisol during the Trier Social Stress test (TSST).

Annals of the New York Academy of Sciences, Volume 1167, Issue Values, Empathy, and Fairness across Social Barriers **(p 87-102)**

A AVPR1A ASSOCIATION THAT REALLY GETS YOUR ATTENTION:
Note: this is a DZ twin study

Genetic variation in the vasopressin receptor 1a gene (*AVPR1A*) associates with pair-bonding behavior in humans

Hasse Walum*†‡, Lars Westberg†§, Susanne Henningsson§, Jenae M. Neiderhiser¶, David Reiss‖, Wilmar Igl*, Jody M. Ganiban**, Erica L. Spotts††, Nancy L. Pedersen*, Elias Eriksson§, and Paul Lichtenstein*

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Edited by Solomon H. Snyder, Johns Hopkins University School of Medicine, Baltimore, MD, and approved July 14, 2008 (received for review March 28, 2008)

Pair-bonding has been suggested to be a critical factor in the evolutionary development of the social brain. The brain neuropeptide arginine vasopressin (AVP) exerts an important influence on pair-bonding behavior in voles. There is a strong association between a polymorphic repeat sequence in the 5′ flanking region of the gene (*avpr1a*) encoding one of the AVP receptor subtypes (V1aR), and proneness for monogamous behavior in males of this species. It is not yet known whether similar mechanisms are important also for human pair-bonding. Here, we report an association between one of the human *AVPR1A* repeat polymorphisms (RS3) and traits reflecting pair-bonding behavior in men, including partner bonding, perceived marital problems, and marital status, and show that the RS3 genotype of the males also affects marital quality as perceived by their spouses. These results suggest an association between a single gene and pair-bonding behavior in humans, and indicate that the well characterized influence of AVP on pair-bonding in voles may be of relevance also for humans.

Table 3. Effect of 0, 1 or 2 334 alleles on male reports on the Partner Bonding Scale, marital crisis, and marital status

Measure	Number of 334 alleles: 0	1	2	*df*	*F*	*P*
Mean score for the Partner Bonding Scale in the three groups						
Partner Bonding Scale	48.0 (6.50)	46.3 (6.16)	45.5 (6.71)	2, 143	8.40	0.0004
Frequency and column-wise percentage of subjects reporting marital crisis/threat of divorce in the three groups						
Have you experienced marital crisis or threat of divorce during the last year?						
No	469 (85%)	277 (84%)	27 (66%)	2, 143	5.00	0.008
Yes	81 (15%)	51 (16%)	14 (34%)			
Frequency and column-wise percentage of subjects being married or cohabiting in the three groups						
Marital status						
Married	457 (83%)	275 (84%)	28 (68%)	2, 143	4.36	0.01
Cohabiting	96 (17%)	52 (16%)	13 (32%)			

Values for the Partner Bonding Scale are means with standard deviation in brackets.

Table 4. Association between 334 alleles in men and their wives' reports of marital qualities

Quality		No 334 (mean)	One or two 334 (mean)	β	*df*	*F*	*P*
Affectional expression	Unadjusted	18.0 (2.99)	17.4 (2.92)	−0.64	1, 113	10.08	0.002
	Adjusted	—	—	−0.39	1, 111	4.30	0.04
Dyadic consensus	Unadjusted	65.4 (8.11)	63.9 (8.57)	−1.46	1, 117	6.92	0.01
	Adjusted	—	—	−0.82	1, 115	2.46	0.12
Dyadic cohesion	Unadjusted	19.5 (4.34)	18.9 (4.10)	−0.60	1, 116	4.27	0.04
	Adjusted	—	—	−0.20	1, 114	0.53	0.47
Dyadic satisfaction	Unadjusted	43.3 (3.14)	43.2 (2.92)	−0.12	1, 111	0.49	0.49

Mean, Mean value on the outcome for the different DAS Scales for wives with standard deviation within brackets. Adjusted, Analysis with the Partner Bonding Scale included as a covariate. The category of subjects not carrying any 334 allele was used as reference group when constructing the regression estimates (β). Analyses of adjusted values were only performed for the scales that were significantly associated with the 334 allele in the unadjusted analysis.

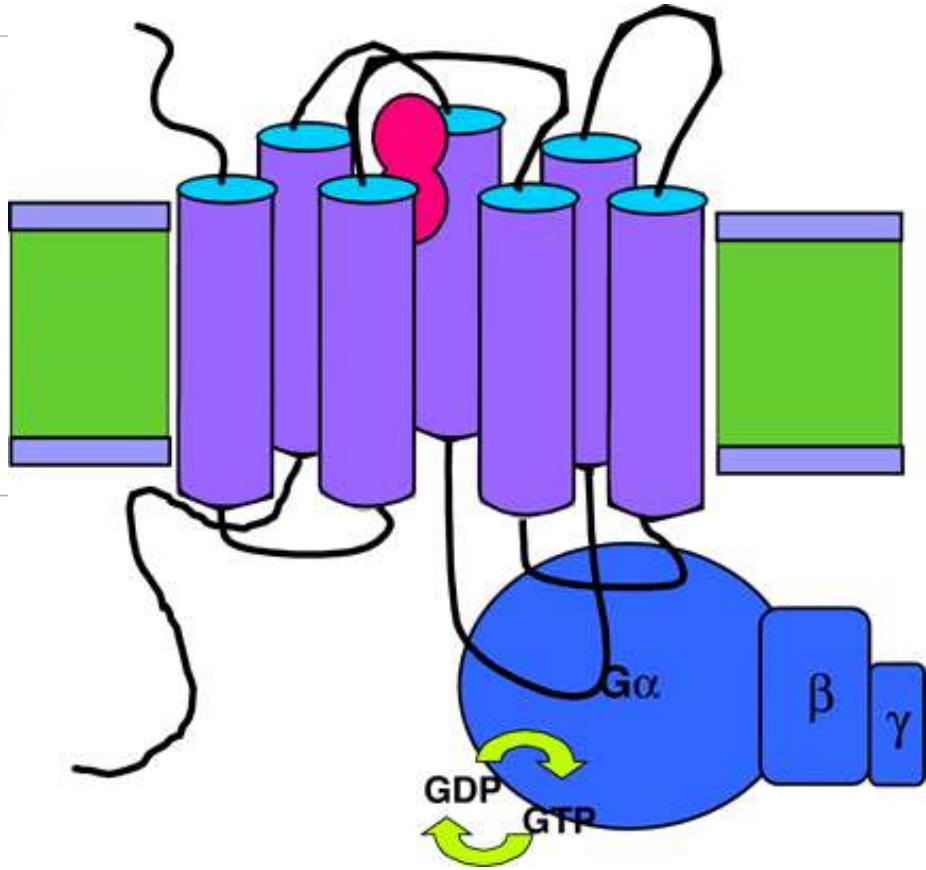
Overall effect size for RC334 on marital success was 0.27 = small / moderate

CLEARLY, THIS IS ONE NEUROPEPTIDE RECEPTOR WE WANT TO KNOW MORE ABOUT!

Vasopressin receptor

From Wikipedia, the free encyclopedia

A **vasopressin receptor** is one of the cell surface receptors which binds vasopressin.[1][2]



http://www.life.illinois.edu/xiang/images/gpcr.gif

Contents [hide]

Subtypes

Humans express three subtypes: 1A, 1B and 2[2]

Receptor	Gene	G protein	Functions
Arginine vasopressin receptor 1A	AVPR1A	G_q	Vasoconstriction
Arginine vasopressin receptor 1B also called *Arginine vasopressin receptor 3*	AVPR1B	G_q	Neural
Arginine vasopressin receptor 2	AVPR2	G_s	Antidiuretic

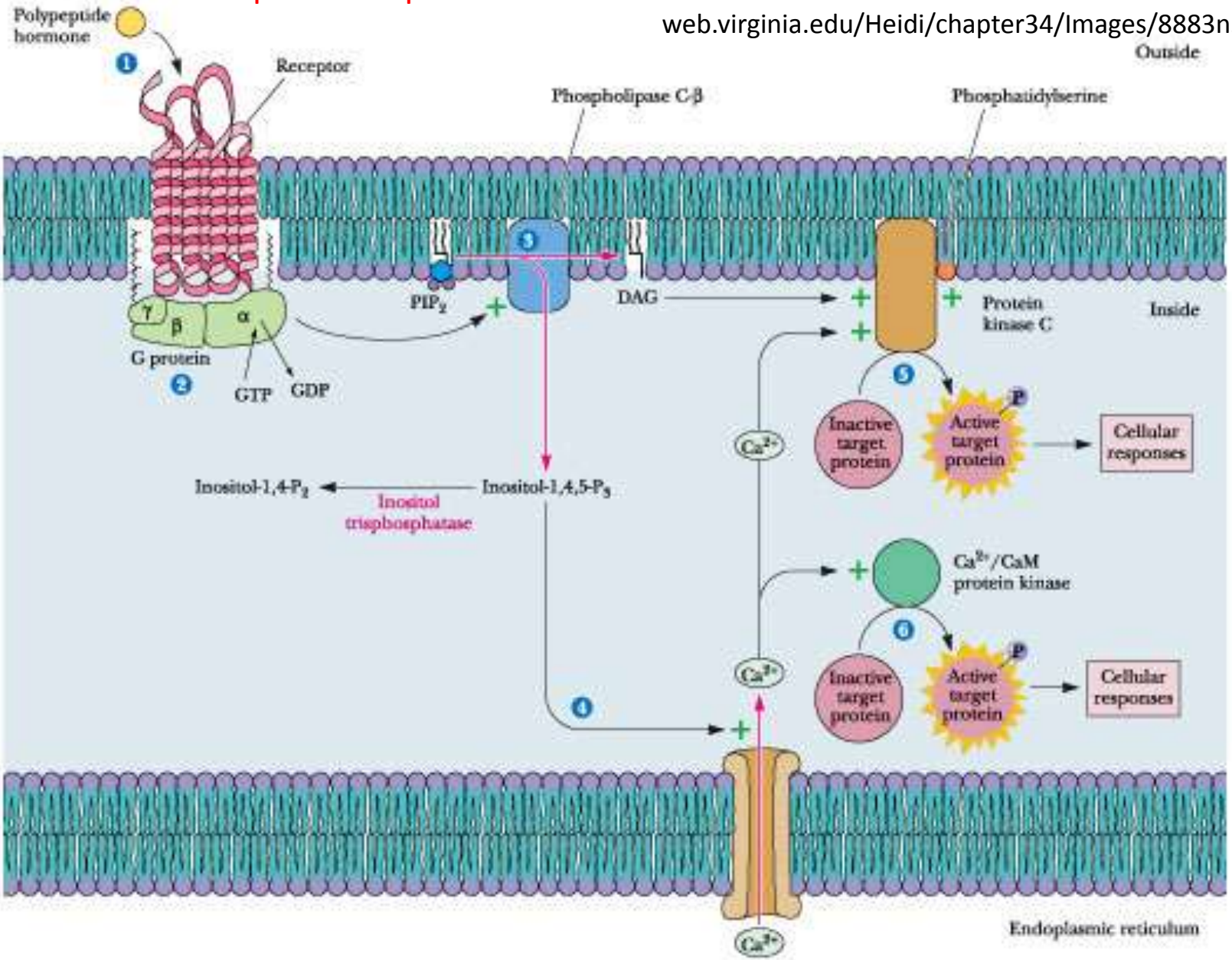
Function [edit]

Although all three of these proteins are G-protein coupled receptors (GPCRs), activation of AVPR1A and AVPR1B stimulate phospholipase C, while activation of AVPR2 stimulates adenylate cyclase.[2] These three receptors for vasopressin have unique tissue distributions. AVPR1A are expressed in vascular smooth muscle cells, hepatocytes, platelets, brain cells, and uterus cells. AVPR1B are expressed in cells of the anterior pituitary and throughout the brain, especially in the pyramidal neurons of the hippocampal CA2 field. AVPR2 are expressed in the kidney tubule, predominantly in the distal convoluted tubule and collecting ducts, in fetal lung tissue and lung cancer, the last two being associated with alternative splicing. AVPR2 is also expressed in the liver where stimulation releases a variety of clotting factors into the bloodstream. In the kidney, AVPR2's primary function is to respond to arginine vasopressin by stimulating mechanisms that concentrate the urine and maintain water homeostasis in the organism. When the function of AVPR2 is lost, the disease Nephrogenic Diabetes Insipidus (NDI) results.[3]

Generic peptide GPCR.

The exact intracellular signaling mechanisms for the 3 vasopressin receptors are not yet known, but the the brain receptors do open cation channels as shown

web.virginia.edu/Heidi/chapter34/Images/8883n34_19.jpg



Human *AVPR1A is situated on chromosome 12q14–15 (9).* Whereas there is no sequence in the human *AVPR1A 5 flanking* region homologous to the one found in prairie voles, humans do have three repetitive sequences in this region that are polymorphic: A (GT)25 dinucleotide repeat, a complex (CT)4-TT-(CT)8-(GT)24 repeat (RS3), and a (GATA)14 tetranucleotide repeat (RS1) (10). ..previous studies have revealed associations between *AVPR1A repeat* polymorphisms and autism (11–13), age at first sexual intercourse (14), and altruism (15), suggesting that these repetitive sequences may have an impact on human social behavior.

← What the polymorphism is

What the polymorphism might do (main implication: more AVP 1a receptors in 334 carriers) →

Although the functional importance of the RS3 polymorphism of the *AVPR1A* remains to be clarified, an association between the length of the RS3 repeat and the amount of hippocampal mRNA in human postmortem tissue has been reported (15). Moreover, a recent study in healthy subjects suggests that the 334 allele is associated with increased activation of amygdala, a brain region known to be of importance for pair-bonding behavior (17). The conclusion of our study (that the 334 allele of the RS3 polymorphism influences brain function) is well in line with previous observations.

Ann N Y Acad Sci. 2009 Jun;1167:87-102.

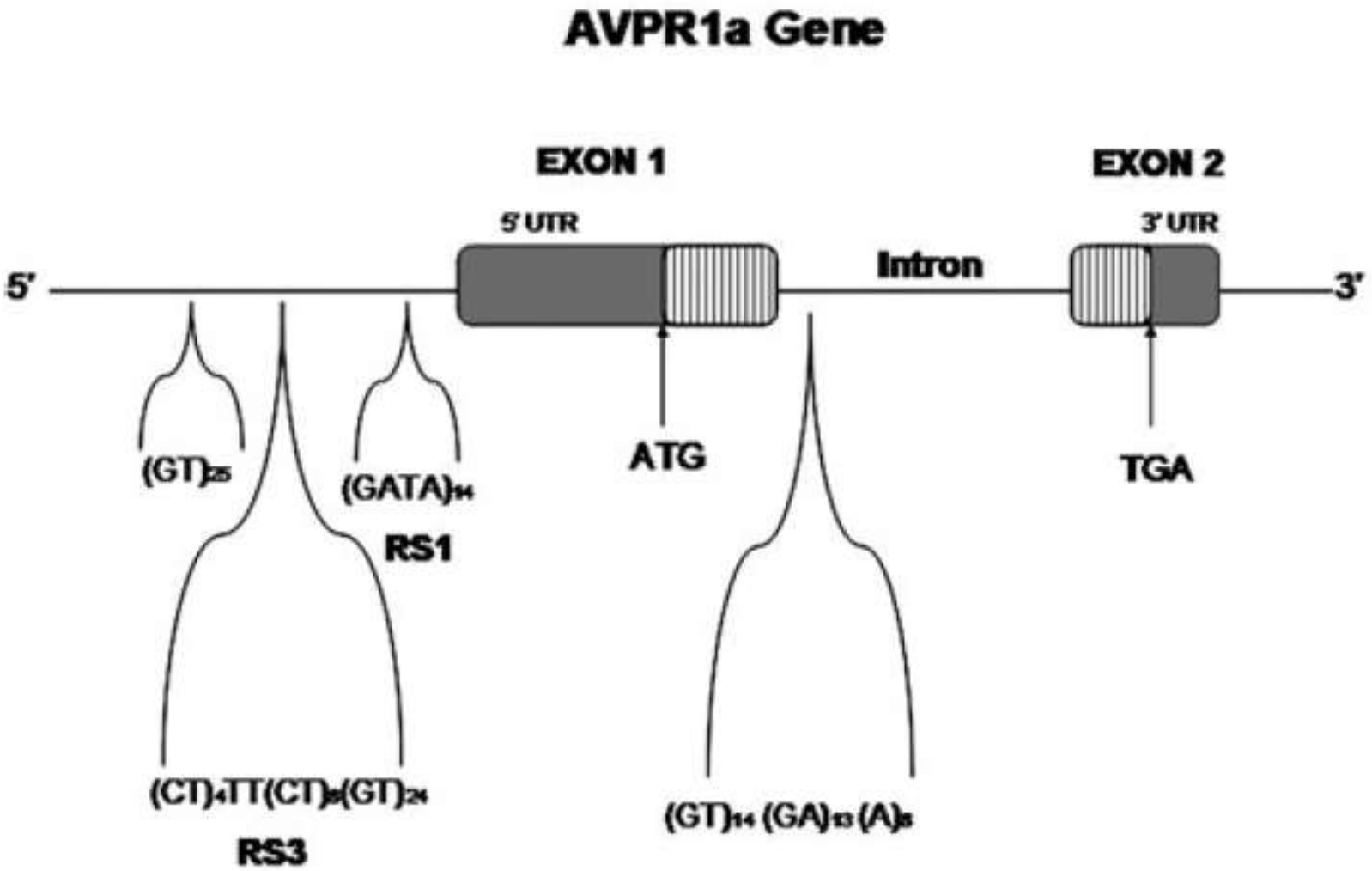


Figure 1. Location of arginine vasopressin receptor 1a (AVPR1a) microsatellite repeats. The start site of protein synthesis is represented by ATG. The gene is located on chromosome 12 q. RS1 & RS3 are promotor repeat regions.

WHERE ARE THESE RECEPTORS IN THE BRAIN? → PMID: 19539696
But, there are HUGE species differences

Neuroscience Letters 461 (2009) 217–222

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Distribution of vasopressin and oxytocin binding sites in the brain and upper spinal cord of the common marmoset

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ABSTRACT

The aim of this study was to label selectively and to map central vasopressin (AVP) and oxytocin (OT) binding sites in the common marmoset. [^{125}I]VPA, a compound selective in rodents and human for the AVP V_{1a} receptor, yielded the same labeling pattern as [^{3}H]AVP, thus suggesting that most AVP receptors present in the marmoset brain are of the V_{1a} subtype. Numerous areas exhibited AVP binding sites, among which the olfactory bulb, the accumbens nucleus, the bed nucleus of the stria terminalis, the hypothalamic suprachiasmatic, arcuate and ventromedial nuclei, the medial amygdaloid nucleus, the nucleus of the solitary tract and the cerebral cortex. Binding sites for [^{125}I]OTA, a selective OT receptor antagonist in rat and human, were markedly less abundant than [^{125}I]VPA ones, and, to a few exceptions, expressed in different areas. Neither AVP, nor OT binding sites were detected in the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei identified by neurophysin immunoreactivity. Marked species-related differences were observed in the distribution of both AVP and OT binding sites. Altogether, our data provide a morphological basis to investigate the function of central AVP and OT in the marmoset.

Neuron. 2010 Mar 25;65(6):768-79.

The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior.

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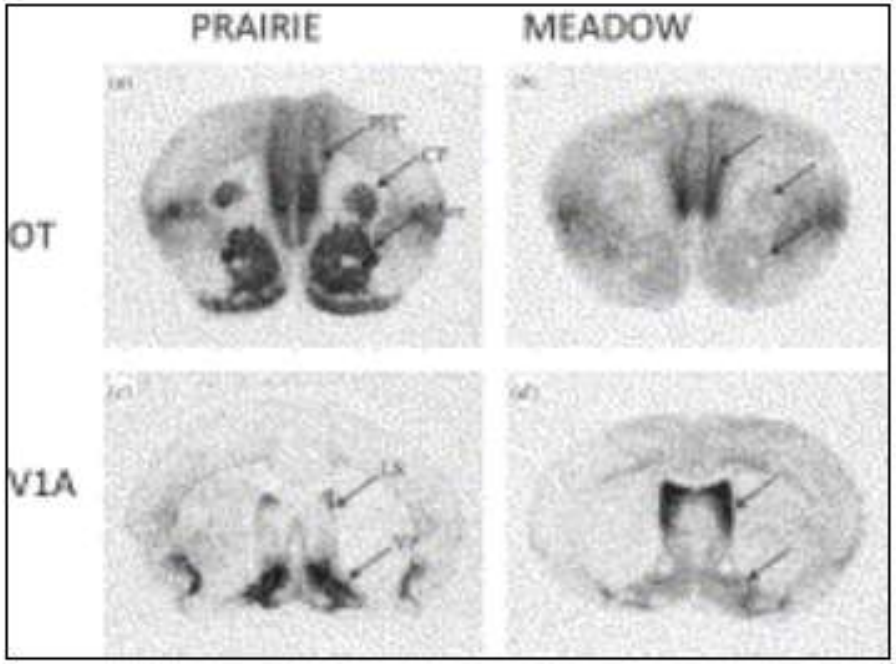

HUGE species differences in AVPR1A distribution and density

Figure 2. Contrasting Distribution of Oxytocin and Vasopressin V1a Receptors to Prairie (Monogamous) and Meadow (Promiscuous) Voles

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Review

Overview of cellular electrophysiological actions of vasopressin

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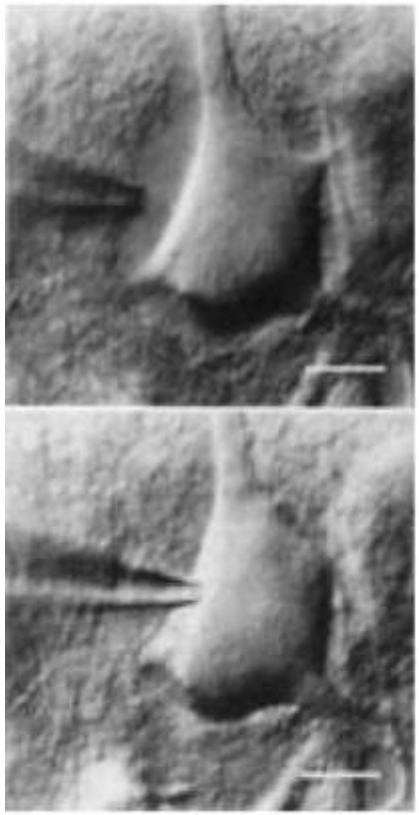
Available online 30 January 2008



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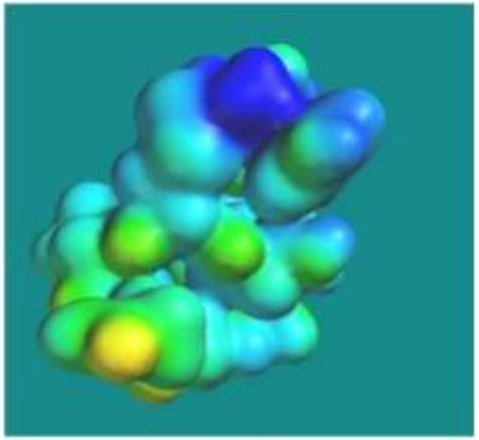
Group leader: Mario Raggenbass

Group name: Neuropeptide and Neurotransmitter physiology

Affiliation: Medical Sciences

Research activities:



The nonapeptide vasopressin acts both as a hormone and as a neurotransmitter/neuromodulator. As a hormone, its target organs include kidney, blood vessels, liver, platelets and anterior pituitary. As a neurotransmitter/neuromodulator, vasopressin plays a role in autonomic functions, such as cardiovascular and temperature regulation, and is involved in complex behavioral and cognitive functions, such as sexual behavior, pair-bond formation and social recognition. Vasopressin exerts its effects by stimulating receptors of the G protein-coupled family. At the neuronal level, vasopressin enhances membrane excitability and modulates synaptic transmission. In particular, vasopressin exerts a powerful excitatory action on brainstem and spinal motoneurons. This effect is due to the generation of a sustained cationic inward current that is TTX-insensitive, sodium- and voltage-dependent and is modified by extracellular calcium. A major unsolved problem is: what's the second messenger responsible for the neuronal action of vasopressin? The main objective of our research program is to characterize the intracellular signaling pathway linking vasopressin receptors to the nonspecific cation channels whose opening is responsible for the peptide-induced excitation in motoneurons. These studies should help elucidate the role played by central vasopressin in the control of motor activity.

Functions of vasopressin in the CNS (from Raggenbass)

Autonomic functions:

- cardio- vascular regulation
- temperature regulation

behavioral and cognitive functions:

- sexual behavior
- memory processes
- pair-bond formation
- fatherhood behavior
- anxiety and depression
- social recognition

Physiological functions:

- Excites spinal motor neurons through V1A receptors in brainstem and spinal cord

HOW DOES VASOPRESSIN EXCITE NEURONS? THAT IS THE CELLULAR QUESTION

Clues from published experiments (Quoted from Raggenbass)- REQUIRES KNOWLEDGE (E.G., OF TOXIN MECHANISMS) AND SOPHISTICATED ELECTROPHYSIOLOGICAL REASONING:

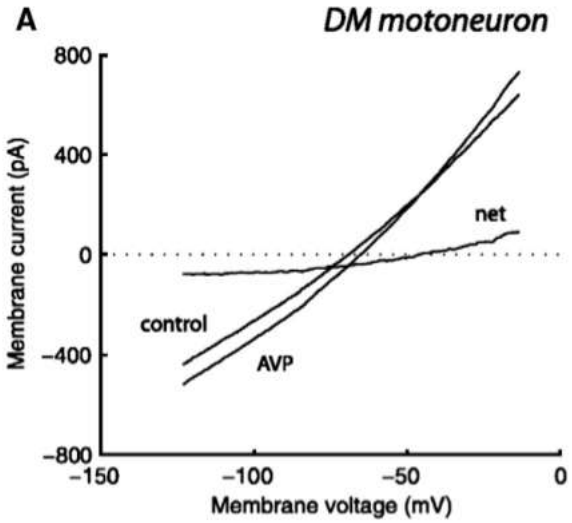
In facial motoneurons, vasopressin acted by generating a sustained cationic inward current, which was tetrodotoxin-insensitive [SOMEONE EXPLAIN 1] voltage gated [SOMEONE EXPLAIN 2] and modulated by extracellular Ca2+ [SOMEONE EXPLAIN 3]

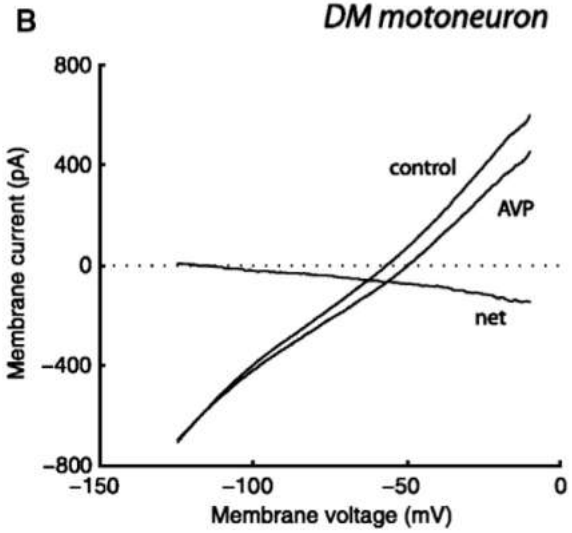
In hypoglossal motoneurons, the vasopressin-evoked current persisted in the presence of blockade of potassium channels [SOMEONE EXPLAIN 4] , and reversed in polarity around − 15 mV, again suggesting the involvement of a cation conductance [SOMEONE EXPLAIN 5]

By contrast, in spinal motoneurons located at the thoracolumbar level, the vasopressin-induced inward current appeared to arise predominantly through reduction of a potassium conductance [SOMEONE EXPLAIN 6]

whole-cell recordings obtained from thoracic sympathetic preganglionic neurons of young rats showed that, by binding to vasopressin V1A receptors, vasopressin induced a tetrodotoxin-resistant inward current that was in part mediated by pertussin toxin-sensitive G protein activation [SOMEONE EXPLAIN 7]

Current–voltage relationships suggest that the peptide influenced two distinct conductances: it suppressed a Ba2+-sensitive K+ conductance and evoked a non-specific cationic conductance that reversed in polarity at around −40mV, displayed inward rectification, but was distinct from Ih, a hyperpolarization-activated cationic current. [SOMEONE EXPLAIN 8]





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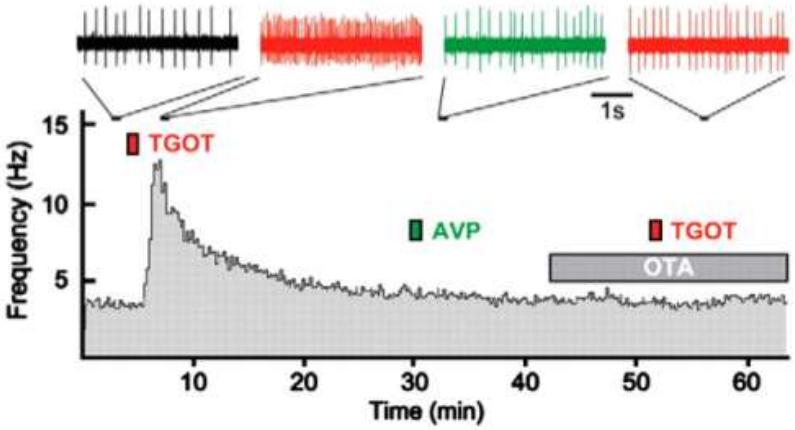

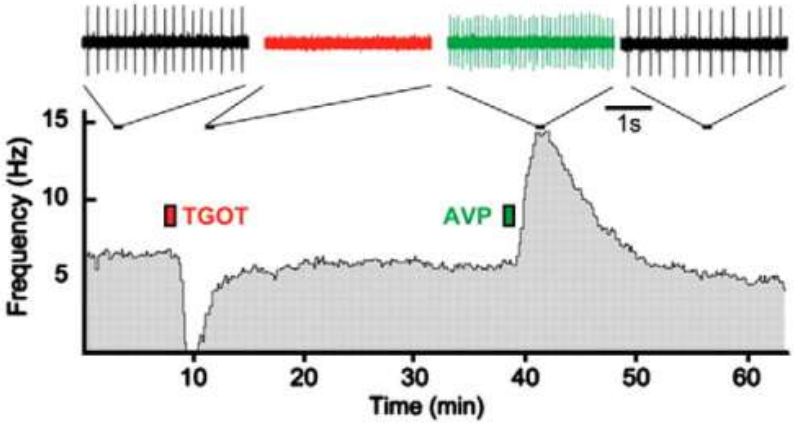

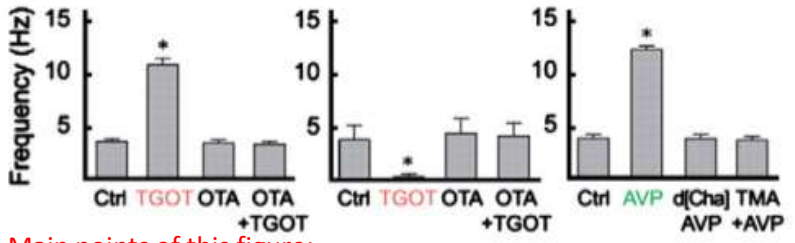

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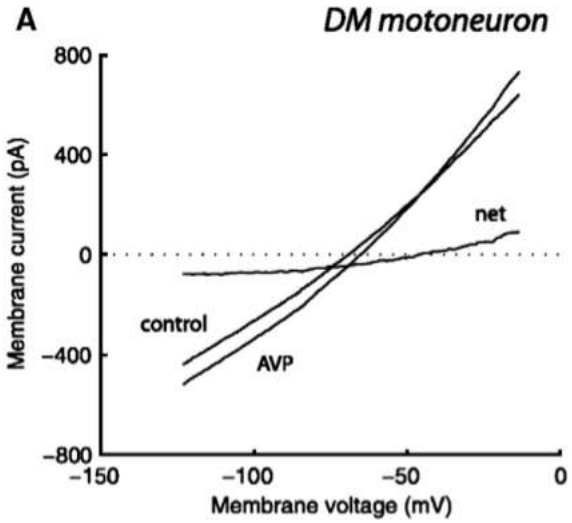
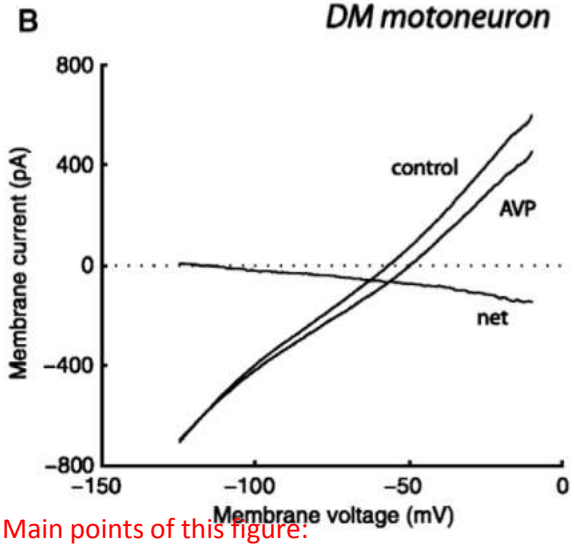


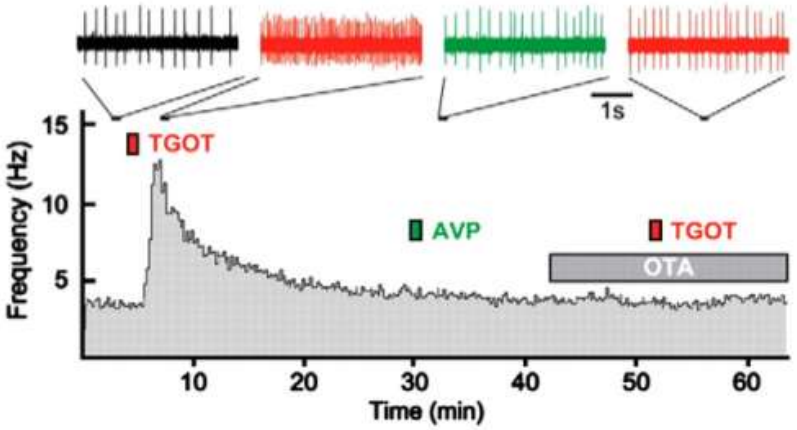


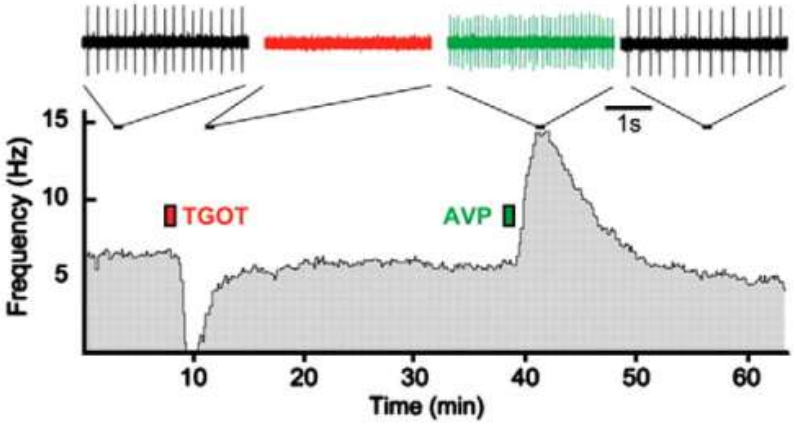
Main points of this figure:

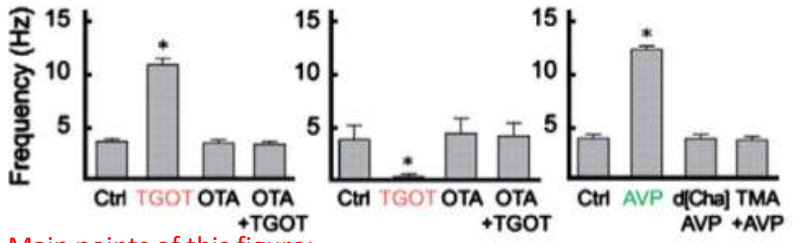
This figure confused me! These may be the points, but I don't see exactl how they're illustrated in the plots

Top: AVP receptors contribute to the inward current produced in some motor neurons by voltage step, probably by opening cation currents

Bottom: Different motor neurons have different responses to AVP. This one might be more consistent with inactivating resting K+ currents that activating cation currents







Main points of this figure:

1. OT and AVP may have opposing effects on central amygdala activation
2. Different AVP receptors are highly selective for their ligand, so my have different functions

Main points of this figure:

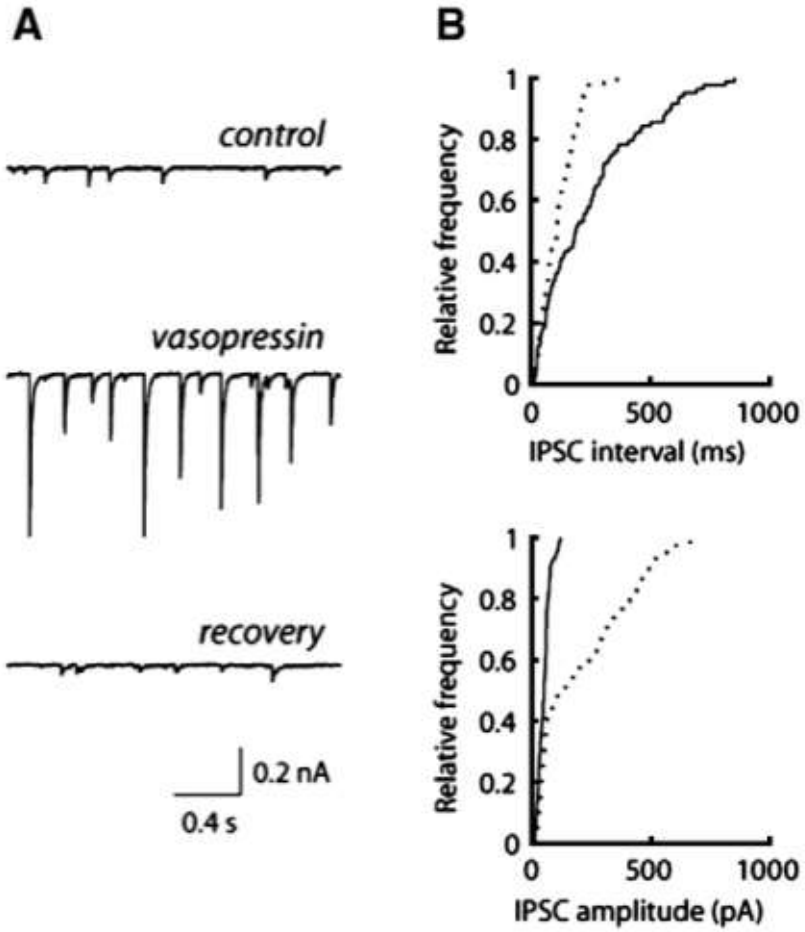


Fig. 3. Vasopressin enhances the frequency and amplitude of spontaneous inhibitory postsynaptic currents in a lateral septal neuron. (A) Current traces, recorded in the voltage-clamp mode, in control conditions, in the presence of vasopressin (0.2 μM) and following washout of the peptide (recovery). (B, top panel) Cumulative plot of the inhibitory postsynaptic current interevent interval distribution obtained in control conditions (continuous line) and in the presence of vasopressin (dotted line). (B, bottom panel) Cumulative plot of the inhibitory postsynaptic current amplitude distribution obtained in control conditions (continuous line) and in the presence of vasopressin (dotted line).

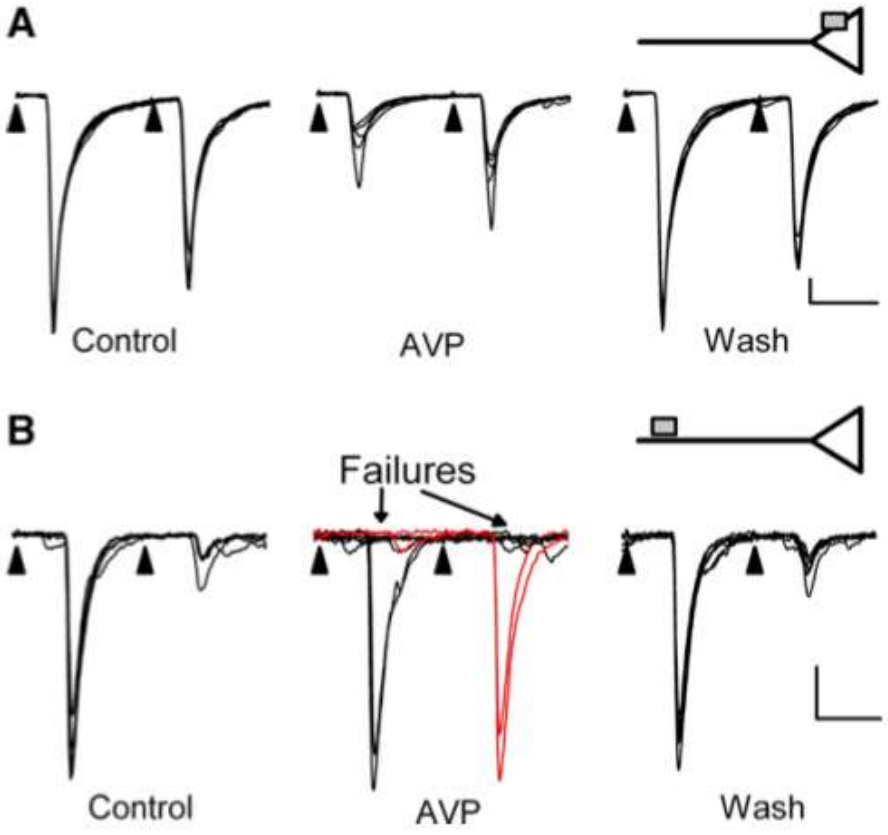
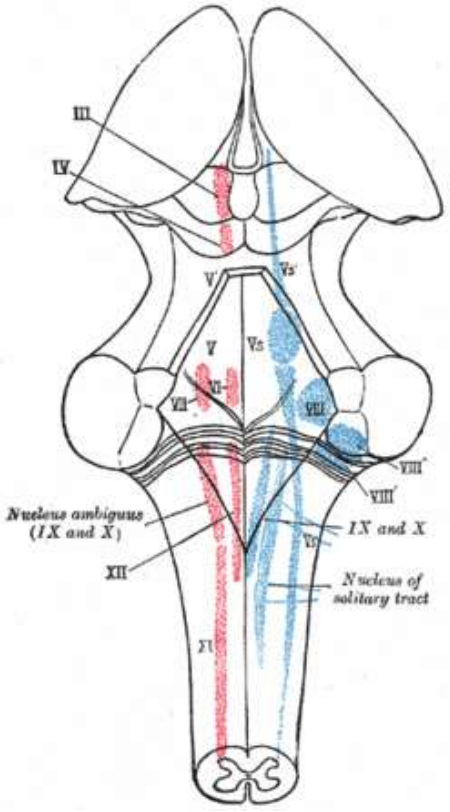


Fig. 4. In the nucleus of the solitary tract, vasopressin (AVP, 3 μM) inhibits solitary tract transmission either by depressing solitary tract-excitatory postsynaptic current amplitudes (A) or by inducing intermittent solitary tract-excitatory postsynaptic current failures (B). Reproduced with permission from Bailey et al. (2006), copyright by the Society for Neuroscience.

Main points of this figure:



(WIKI): The nucleus of the solitary tract, or NTS (Latin: ***nucleus tractus solitarii***), is located along the length of the medulla (with a small portion in the lower pons). The solitary tract runs in the middle of the nucleus, creating a speck of white matter (axons of the tract), surrounded by grey matter (the nucleus). This stands out on a stained section, which is where the name solitary comes from.

(Quoted from Raggenbass)

Key questions remaining about cellular mechanisms of neuronal vasopressin signaling:

(i) What is the exact nature of the cation channel and of the resting K+ channel which are activated, respectively suppressed, following vaso- pressin binding to vasopressin V1A receptors?

(ii) What is the intracellular signaling pathway responsible for the excitatory action of vasopressin on motoneurons?

On the dual excitatory / inhibitory actions of AVP:

Recent studies on the mechanism of action of vasopressin, performed at the cellular level or at the level of local neuronal circuitry, have revealed a recurrent theme. Vasopressin appears to exert its effects, at least in some central nervous structures, in a dual, apparently paradoxical manner: (i) by acting postsynaptically, it causes excitation in a specific neuronal population; (ii) by acting indirectly, it causes inhibition in this same neuronal population. What may be the functional significance of these contrasting actions? A possible scenario could be the following. On one hand, the membrane properties of the target neurons are modified by vasopressin in such a way that these neurons tend to be excited, i.e. to depolarize. On the other hand, the membrane potential of these same neurons tends to remain at or near its original value because of the vasopressin-induced increase in synaptic inhibition (or decrease in synaptic excitation). By virtue of this circuitry, vasopressin has the potential capability of modifying the bioelectrical properties of responsive neurons without significantly altering their membrane potential. In other words, vasopressin would act more as a neuromodulator rather than a classical neurotransmitter.

So is blocking vasopressin a good idea?
Some drug companies have bet that it is→

vs SSR149415

Naunyn Schmiedebergs Arch Pharmacol. 2009 Jan;379(1):101-6. Epub 2008 Jul 31.

SSR149415, a non-peptide vasopressin V1b receptor antagonist, has long-lasting antidepressant effects in the olfactory bulbectomy-induced hyperactivity depression model.

Breuer ME, van Gaalen MM, Wernet W, Claessens SE, Oosting RS, Behl B, Korte SM, Schoemaker H, Gross G, Olivier B, Groenink L.

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Abstract

Olfactory bulbectomy (OBX) in rats causes several behavioral and neurochemical CNS changes, reminiscent of symptoms of human depression. Such depression-like behavior after OBX can be reversed with antidepressants. Recently, a connection between the vasopressin 1b (V1b) receptor and the development of depression has been suggested; therefore, a vasopressin V1b receptor antagonist (SSR149415) was investigated in the OBX model. Male rats received olfactory bulbectomy or sham surgery. After recovery, animals received 14 consecutive daily doses of SSR149415 (10 or 30 mg/kg), imipramine (20 mg/kg), or vehicle (5% hydroxy-propyl methylcellulose). Animals were tested in an open field after acute treatment, on days 7 and 14 of treatment and 1 week after cessation of treatment. Similar to imipramine, repeated, but not acute, administration of SSR149415 completely reversed OBX-induced hyperactivity, leaving activity in shams unaffected. This reversal of OBX-induced hyperactivity in the SSR149415 treated rats was still present 7 days after cessation of treatment. Although the behavioral effects of treatment with SSR149415 were specific for the OBX animals, adrenal gland weights were reduced in both sham and OBX animals treated with 30 mg/kg SSR149415. Chronic but not acute administration of SSR149415 normalizes OBX-induced hyperactivity up to 1 week after cessation of treatment, suggesting that a V1b receptor antagonist may have long-lasting antidepressant activity.

Nelivaptan

From Wikipedia, the free encyclopedia

Nelivaptan (INN[1]), codenamed **SSR-149,415**, is a selective and orally active non-peptide vasopressin receptor antagonist selective for the V1b subtype.[2] The drug had entered clinical trials for treatment of anxiety and depression.[3] In July of 2008, Sanofi-Aventis announced that further development of this drug had been halted.[4]

References [edit]

1. ^ World Health Organization (2007). "International Nonproprietary Names for Pharmaceutical Substances (INN). Proposed INN: List 98". *WHO Drug Information* **21** (4): 341.
2. ^ Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B, Maffrand JP, Soubrie P (2002). "Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders". *Proc. Natl. Acad. Sci. U.S.A.* **99** (9): 6370–5. doi:10.1073/pnas.092012099. PMID 11959912.
3. ^ Serradeil-Le Gal C, Wagnon J, Tonnerre B, Roux R, Garcia G, Griebel G, Aulombard A (2005). "An overview of SSR149415, a selective nonpeptide vasopressin V(1b) receptor antagonist for the treatment of stress-related disorders". *CNS drug reviews* **11** (1): 53–68. PMID 15867952.
4. ^ "Second-quarter 2008 results". *Press Release*. Sanofi-Aventis. 2008-07-31. Retrieved 2009-06-10. "It has been decided to discontinue the development of amibegron and SSR 149415 (a V1B receptor antagonist)."

Central Nervous System

Paris, July 31, 2008

Eplivanserin is a compound in a new class, 5HT2-A antagonists, intended to treat sleep disorders. It improves the quality of sleep by reducing the number and duration of WASO (Wake time After Sleep Onset) events in patients with fragmented sleep patterns, with no residual effects reported to date.
Submissions for the approval of eplivanserin are due to be filed with the authorities in the fourth quarter of 2008.

DANCE PHENOTYPE

Saredutant: Results from the MAGENTA study, evaluating the maintenance of the effects of saredutant in the treatment of major depressive disorders, confirmed the product's good long-term safety profile. However, the MAGENTA study also showed that relapse was not significantly reduced versus placebo when patients who had responded to saredutant after 3 months had their treatment extended to 12 months.
Analysis of all other saredutant short term studies studies revealed a benefit for patients with major depressive disorders based on the HAM-D scale.
The decision on submitting saredutant for regulatory approval will depend on the results of two ongoing trials assessing the product in combination with the selective serotonin reuptake inhibitors (SSRIs) escitalopram and paroxetine, which are due to be completed in the first half of 2009.

Teriflunomide is a potential oral treatment for multiple sclerosis, with a targeted efficacy profile similar to interferons on relapse and progression of disability, but with a better safety. Enrolment of the 1,080 patient population in the TEMSO phase III placebo-controlled trial evaluating teriflunomide as monotherapy is now complete.

It has been decided to discontinue the development of **amibegron** and SSR 149415 (a V1B receptor antagonist).

But there's hope for us human men even without AVP antagonists…

Looking at differences in AVP and social behavior across species, it seems that evolutionary selection can easily tinker with social behavior by altering the number and distribution of AVP receptors in the brain. AVP receptor density is the main difference, for example, between closely related montane and prairie voles that have very different social behaviors. This is also consistent with the idea that RS 334 allele in humans that's associated with weaker pair bonding has its effect by reducing the number of AVP receptors in the brain. So as long as women do their part and select for pair bonding men, men will evolve into the devoted husbands they always claim they will be.