

## INTRODUCTION

Monogamy is a sexual and affective social bond characterized by the formation of a relationship of exclusivity for a partial period of time or for life. Social affective relationships can have considerable influence in our psychological, physiological and behavioral functions, and for this reason, many efforts have been made to study the neurobiological mechanisms that may regulate them. Recent experiments have reported that vasopressin and oxytocin, two neuropeptides better known for his peripheral roles in parturition, lactation (oxytocin), vasoconstriction and water retention (vasopressin), seem to exert a strong influence on the formation of this type of bond.

## MONOGAMY IN VOLES

Prairie voles (*Microtus ochrogaster*), Montane voles (*Microtus montanus*) and Meadow voles (*Microtus pennsylvanicus*) are three different species of rodent mammals that inhabit North America, particularly the United States and Canada. Despite belonging to the same genus, there are important differences in their social behavior, specially in pair bond formation.

Prairie vole is monogamous while Montane and Meadow voles are promiscuous. This difference allows them to be considered an excellent animal model to study the neurobiological mechanisms of monogamous behavior.

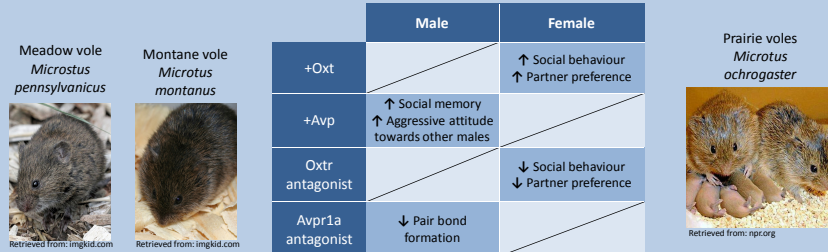


Fig 1. Significant results of pharmacological experiments in prairie voles. Oxytocin and an antagonist of oxytocin is administered to females, while vasopressin and an antagonist of vasopressin is given to males.

## VASOPRESSIN IN MONOGAMY Animal model

In monogamous voles, there's a microsatellite sequence of 428 bp DNA in the 5' flanking region of Avpr1a, longer than in promiscuous voles.

Gene transfer experiments have shown that if the gene Avpr1a (including microsatellite DNA sequence) of monogamous voles is injected to promiscuous voles, the pattern of receptor distribution obtained later became similar to those found in monogamous voles, and the genetically modified voles behave in a more monogamous way.

## OXYTOCIN IN MONOGAMY Animal model

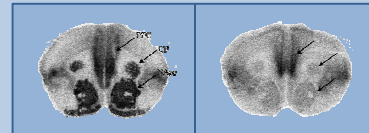


Fig 8. Comparison of brain distribution of oxytocin receptors between females of promiscuous and monogamous voles. Nacc: Nucleus Accumbens; PFC: Pre-frontal cortex; CP: Caudate putamen. Caudate putamen is related with the reward system, while Nucleus accumbens and Pre-frontal cortex are directly involved in it.

## Human model

In humans, Single Nucleotide Polymorphisms (SNP) candidate to be studied are found throughout the OXTR gene.

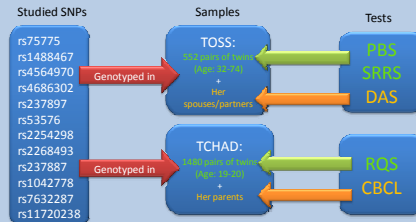


Fig. 12. TOSS: Twin and Offspring Study in Sweden; PBS: Partner bonding scale; SRRS: Social Readjustment Rating Scale; DAS: Dyadic Adjustment Scale. DAS is applied to the spouses/partners of the subjects about the subjects, and it has 4 subscales: Dyadic Consensus, Dyadic Satisfaction, Dyadic Cohesion, and Affective Expression. TCHAD: Twin study of Child and Adolescent Development; RQS: Relationship Quality Survey; CBCL: Child Behavioral Checklist.

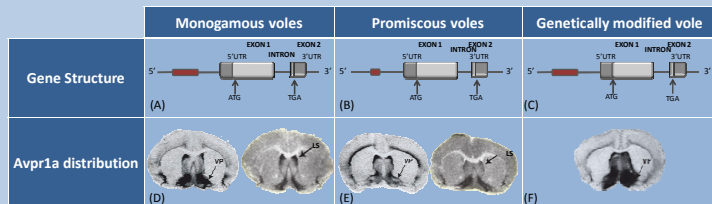


Fig 2. Comparison of gen structure (A) (B), and brain distribution (C) (D) of vasopressin receptors between males of monogamous and promiscuous voles. (C) (F): Gen transfer experiment and results in Avpr1a brain distribution. VP: Ventral pallidum; LS: Lateral septum. Ventral pallidum and lateral septum are involved in the reward system.

## Human model

In humans, there are 3 repetitive sequences at the beginning of the Avpr1a that are polymorphic (fig.3). Several studies about monogamy have studied them to detect their effects on pair bond formation regulation.

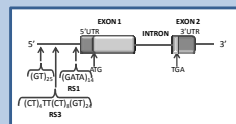


Fig 3. AVPR1a gene structure in humans, with the 3 polymorphic sequences.

	Men				Women			
Repeat	df	F	P	Repeat	df	F	P	
GT <sub>25</sub>	21, 148	0.39	0.99	GT <sub>25</sub>	18, 138	1.05	0.41	
GT <sub>30</sub>	92	9.9	47.6 (1.18)	GT <sub>30</sub>	1, 37	0.21	0.65	
GT <sub>32</sub>	128	13.8	47.5 (6.45)	GT <sub>32</sub>	1, 50	0.06	0.81	
GT <sub>33</sub>	19, 137	2.48	0.001	GT <sub>33</sub>	21, 166	1.19	0.27	

Fig 4. Associations between polymorphisms and outcome for PBS. We find a significant global P value in the R33 polymorphism and the outcome of the PBS for men.

Allele	Freq	Percent	Mean	df	F	P
320	21	2.3	48.8 (6.21)	1, 12	1.52	0.24
330	170	18.3	48.3 (6.21)	1, 77	4.73	0.03
340	263	28.4	47.5 (6.50)	1, 106	0.40	0.53
342	30	3.2	47.0 (4.49)	1, 12	0.05	0.82
344	23	2.5	45.6 (6.43)	1, 8	1.64	0.24
346	126	13.6	46.7 (6.87)	1, 60	1.30	0.26
348	37	4.0	47.9 (6.47)	1, 16	0.36	0.55

Fig 5. Associations between alleles of R33 and outcome for PBS. We find a significant global P value between the allele 334 and a lower score in PBS.

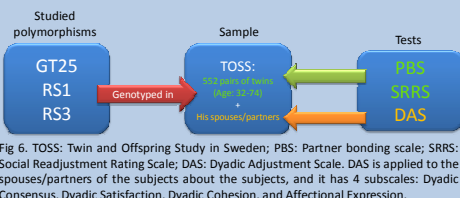


Fig 6. TOSS: Twin and Offspring Study in Sweden; PBS: Partner bonding scale; SRRS: Social Readjustment Rating Scale; DAS: Dyadic Adjustment Scale. DAS is applied to the spouses/partners of the subjects about the subjects, and it has 4 subscales: Dyadic Consensus, Dyadic Satisfaction, Dyadic Cohesion, and Affective Expression.



Fig 7. Significant results comparison between carriers and non-carriers of allele 334 submitted to different parameters of pair bond quality tests.

## CONCLUSION

Neuropeptides vasopressin and oxytocin participate positively in regulating the monogamous behaviour in humans (vasopressin in males and oxytocin in females), improving the quality of partner relationships.

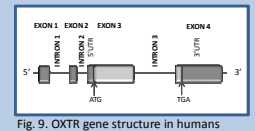


Fig. 9. OXTR gene structure in humans

Snp	TOSS (Partner Bonding Scale)			TCHAD (Relationship Quality Survey)			
	df	F	P	Snp	df	F	P
rs75775	2, 104	1.35	0.26	rs75775	2, 200	1.59	0.21
rs1488467	2, 512	1.51	0.22	rs1488467	2, 171	1.03	0.36
rs4564970	2, 449	2.41	0.09	rs4564970	2, 166	1.26	0.29
rs4686302	2, 102	0.89	0.41	rs4686302	2, 212	2.88	0.06
rs257897	2, 1123	2.70	0.07	rs257897	2, 271	0.25	0.78
rs53576	2, 1119	2.69	0.07	rs53576	2, 263	0.64	0.53
rs2254298	2, 682	1.02	0.36	rs2254298	2, 118	0.50	0.61
rs2268493	2, 1102	1.51	0.22	rs2268493	2, 274	1.30	0.27
rs237887	2, 1114	0.72	0.49	rs237887	2, 282	1.62	0.20
rs1042778	2, 1139	0.92	0.40	rs1042778	2, 279	0.61	0.54
rs7632287	2, 1093	3.88	0.02	rs7632287	2, 238	3.16	0.04
rs11720238	2, 1102	1.09	0.34	rs11720238	2, 204	0.22	0.80

Fig. 10. Associations between SNPs and outcome for PBS and RQS. We found a significant global P value in the rs7632287 and the outcome of the PBS/RQS for women or girls.

A/A (N=8830)	A/G (N=51512)	G/G (N=81017)	df	F	P
56.78 (6.50)	56.46 (6.96)	47.52 (6.48)	1, 1162	7.59	0.006
56.56 (6.40)	56.81 (3.82)	57.81 (3.12)	1, 296	6.27	0.01

Fig. 11. Associations between alleles of rs7632287 and outcome for PBS (1<sup>st</sup> row) and RQS (2<sup>nd</sup> row). We find a significant global P value between carriers of allele A and a lower score in PBS (TOSS) or RQS (TCHAD). \*Analyses were performed by comparing carriers and noncarriers of A allele.

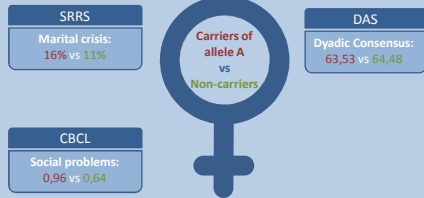


Fig. 13. Significant results comparison between carriers and non-carriers of A allele submitted to different parameters of pair bond quality tests.

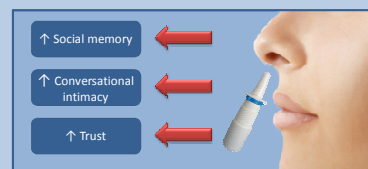


Fig 14. Effects of pharmacological experiments using intranasal oxytocin.

## REFERENCES

Fig 2 (D) (E) (F). Donaldson, Z., & Young, L. (2008). Oxytocin, vasopressin, and the neurogenetics of sociality. *Science*, 322(November 2008), 900-905.

Fig 4. S. Walum, H., & Westberg, L. (2008). Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. *Proceedings of the National Academy of Sciences*, 105(37), 14153-14156.

Fig 8. Hammock, E. A. D., & Young, L. J. (2006). Oxytocin, vasopressin and pair bonding: implications for autism. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 361(1476), 2187-2198.

Fig 10, 11. Walum, H., Lichtenstein, P., Neiderhiser, J. M., Reiss, D., Ganiban, J. M., Spotts, E. L., Westberg, L. (2012). Variation in the oxytocin receptor gene is associated with pair-bonding and social behavior. *Biological Psychiatry*, 71(5), 419-426.