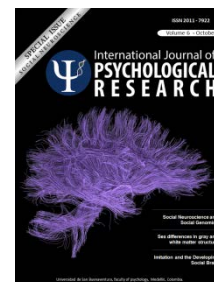




Potential interactions between oxytocin receptor system (OXTR) and candidate genes associated to psychopathy

Probables interacciones entre el receptor de oxitocina (OXTR) y genes candidatos asociados a la psicopatía



Review

Jorge Mauricio Cuartas Arias^{a, b, *} and Carlos Alberto López Jaramillo^b

^a Faculty of Psychology, Universidad de San Buenaventura Medellín, Colombia.

^b Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia.

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ABSTRACT

Psychopathy is the result of a complex interaction between biological and environmental factors; both participate in the final expression of the phenotype and can modulate the variation regarding beginning, deterioration, and severity. Nevertheless, up to now it has not been possible to determine the circumscribed molecular track and its interaction with environmental factors that shape its expression. However, beyond the progresses regarding diagnostic evaluation, there are some difficulties in the construction of a neurobiological model that contributes to differentiate the antisocial behavior. That is why exploring the molecular-genetic, biochemical and hormonal mechanisms involved in the different neuro-physiological tracks modulated by candidate genes could contribute to determine significantly how the neurobiological findings impact the individual differences in the expression of psychopathy. This article aims to go in depth into those neurobiological mechanisms underlying psychopathy from the expression and regulation of the oxytocinergic system.

Key Words:

OXT, OXTR, Oxytocine, Psychopathy, candidate genes, endophenotype

RESUMEN

La psicopatía es el resultado de una compleja interacción de factores biológicos y ambientales, ambos participan en la expresión final del fenotipo y pueden modular la variación en inicio, deterioro y severidad; sin embargo, hasta ahora no se han logrado determinar vías moleculares circunscritas y su interacción con los factores ambientales que modelen su expresión. No obstante, más allá de los avances en la evaluación diagnóstica, hay dificultades en la construcción de un modelo neurobiológico que contribuya a discriminar la conducta antisocial. Por lo tanto, explorar los mecanismos genético-moleculares, bioquímicos y hormonales implicados en las diferentes vías neurofisiológicas moduladas por genes candidatos, podría contribuir significativamente en determinar cómo los hallazgos neurobiológicos impactan las diferencias individuales en la expresión de la psicopatía. Este artículo tiene el propósito de profundizar en aquellos mecanismos neurobiológicos que subyacen a la psicopatía a partir de la expresión y regulación del sistema oxitocinérgico.

Palabras Clave:

OXT, OXTR, oxitocina, psicopatía, genes candidatos, endofenotipo

* **Corresponding author.** Mauricio Cuartas, Faculty of Psychology, Universidad de San Buenaventura, Medellín, Colombia, Mauricio.cuartas@usbmed.edu.co Tel: (57-4) 514 56 00, ext. 4245.



1. INTRODUCTION

Oxytocin (OXT) is a neuropeptide with a hormonal and neurotransmitter role associated initially with milk secretion and the reproductive function in women. It also has a relevant role in the central nervous system and a higher expression in women than men (H. J. Lee, Macbeth, Pagani, & Young, 2009).

Up to now, several studies have indicated the OXT effects in prosocial behaviors, especially in affiliation and empathy (Poulin, Holman, & Buffone, 2012), stress regulation, social interaction, rise and feel of confidence in others (Kumsta & Heinrichs, 2013; Lucas-Thompson & Holman, 2013), and moral behaviour (Pfeiffer, 2013).

These findings about the variable expression of OXT in a cerebral level can configure a neurobiological way to differentiate personality disorders from putative molecular markers that constitute a particular gene and molecular network

2. PERSONALITY AS A DIMENSION

Cloninger (1993) defined personality as a dynamic organization of different psychobiological systems integrated in a neurobiological, interpersonal and affective maturation on the individual that favors the social adaptation. In this perspective, individual differences integrate a dynamic array that incorporates the relation with oneself, the others and the environment, which has an underlying physiological system regulated by genes and the interaction between them and the environment (Aron et al., 2010; Stemmler & Wacker, 2010). Recent researches have reported association between candidate genes and personality disorders. Nevertheless, the clinical analyses to determine a group of symptom, which in diagnosis are gathered into factors to identify circumscribed genetic associations, have not been consistent. Currently, the strategy aims to evaluate different dimensional features that can be determined by several genes, which interact additively or not (J. M. C. Arias, & C. A. P. Acosta, 2011; M. C. Arias, 2011; Cuartas Arias et al., 2011). This alternative may be an interesting strategy to tackle the complexity of behavior. When a genetic polymorphism has been associated with a population, it could not be associated with another ethnic group, which can explain a huge quantity of misunderstanding genetic discoveries. Besides, the presence of pleiotropic and epistatic effects can contribute critically and differentially to the molecular basis of personality. Up to now, some methods to mapping genes in complex diseases, like studies of genetic association, have been advantageous. Even though a large clinical

heterogeneity coexists for psychopathology, these designs can offer a greater statistical robustness when controlling the bias of sample selection and experimental errors in allelic and genotypic frequencies for a particular gene variant.

3. GENETIC ASSOCIATION STUDIES

Association studies are used to determine if there is an epidemiologic relation between one or more genetic variants and a trait, starting from how the frequencies of these variants differ among a group of cases and another of control. However, from this biological point of view, the association has three different interpretations: (i) The polymorphism has a causal role (direct association), (ii) The polymorphism is not causal, but it is in a linkage disequilibrium with the causal variant (indirect association), or (iii) The association is a product of stratification or mixing of population (Spurious association) (Cordell & Clayton, 2005).

The designs for genetic association use different strategies, among them we find the recruitment of large or nuclear families, but this method is difficult, expensive and slow. There also are designs that incorporate unrelated individuals, who are much easier to recruit, but they are susceptible to population stratification. In this regard, there are not studies of families for Personality that have good experimental sensitivity or that have been replicated. These variations can be functional and related to the physiopathology of the disease, but in most cases, they are used to map and locate really relevant sites. A single nucleotide polymorphisms (SNPs) is a variation of the ADN sequence that affects just one nucleotide (adenine (A), thymine (T), cytosine (C), or guanine (G)) of the genome. Each one of these variations should be at least in 1% of the population to be considered as a SNP (Muse, 2004). The SNP candidates are a direct test of association between a functional putative variation and the risk of disease. In this case, it is established in advance a candidate gene based on previous studies or biological experimental evidence. (Tenesa & Dunlop, 2006).

4. OXT GENE AND BEHAVIOR TRAITS AND DISORDERS

The OXT gene has been mapped in the large arm of the chromosome 20 (20p13), which codify for two proteins, oxytocin and neurophysin I. Both are packaged into the neurosecretory vesicles and carried by the axon to the terminal nerve of the neurohypophysis. OXT has three exons, two introns, and currently it has been documented just one

receptor (OXTR), located in the *chromosome 3* (3p25) that has four exons and three introns. Recently, different studies for OXT and OXTR genes have shown association in prosocial, emotional expression, individual differences and autism (Lerer et al., 2008; Tansey et al., 2010; Yrigollen et al., 2008), schizophrenia (Montag et al., 2013; Teltsh et al., 2011), psychopathy (Dadds, Moul, Cauchi, Dobson-

Stone, Hawes, Brennan, Urwin, et al., 2013; Johansson et al., 2012), and so far it has been reported a complete genome for alcohol dependence with depressive syndrome in European - American descent (Edwards et al., 2012). Table 1 presents some of the key findings in 2013 for gene variants in OXT and OXTR in mental disorders and psychopathology (Table 1).

Table 1. Genetic polymorphisms in OXT and OXTR associated with psychiatric disorders

Gene	SNP	Polymorphism	Phenotype	Author
OXTR	rs2254298	A Allele	Autism spectrum disorders	(Bakermans-Kranenburg & van Ijzendoorn, 2013; Saito et al., 2013)
	rs237887	G allele		
OXTR	rs53576	(A > G) change base	Schizophrenia	(Montag, et al., 2013)
	rs237885	(T > G)		
OXTR	rs10427778	TT Genotype	Psychopathy	(Dadds, Moul, Cauchi, Dobson-Stone, Hawes, Brennan, Urwin, et al., 2013)
OXT	rs2740210	A Allele	Depression	(Jonas et al., 2013)
OXTR	rs53576	AA genotype	Anxiety disorders (female subjects)	(Wang et al., 2013)

Association studies of genetic polymorphism in OXT and OXTR for mental disorder published in 2013. The database Medline was used as search criterion; just the research articles in complete text were evaluated (systematic or narrative reviews were not included). Keywords were: OXT, OXTR, genetic polymorphisms, and mental disorders. Only positive results of association in polymorphic variants for OXT and OXTR were taken into account.

5. OXT GENE AND PSYCHOPATHY

In regard to the gene variants effects of OXT and OXTR, there are numerous studies that suggest the modeling of neurocognitive responses such as episodic and spatial memory (H. J. Lee, et al., 2009), decision making (Israel et al., 2009) and monitoring (Meyer-Lindenberg, 2008; Sala et al., 2011). The implications of the OXT system with the association of different genetic polymorphisms for different clinical phenotypes can delineate a way of molecular association that would allow infer a potential phenotype for psychological patterns closely related.

For psychopathology, from the dimensional perspective of personality and using as a model the observed finding for psychopathy, several studies have allowed to associate different SNPs in the OXTR gene and the differential expression of polymorphisms, in particular the G allele of rs 1042778 (Dadds, Moul, Cauchi, Dobson-Stone, Hawes, Brennan, & Ebstein, 2013; Dadds, Moul, Cauchi, Dobson-Stone, Hawes, Brennan, Urwin, et al., 2013), which can modulate processes of protein transduction and transcription in

OXTR. This allelic variant in the receptor has been repeatedly associated with psychopathy and alterations in the inhibitory control (Johansson, et al., 2012; Malik, Zai, Abu, Nowrouzi, & Beitchman, 2012; Montag, Fiebach, Kirsch, & Reuter, 2011). The findings suggest that the presence of this polymorphism reduce the amygdala activation and affect the connectivity in the orbitofrontal and ventromedial cortex, both involved in the moral judgment and the emotional perception (Marsh et al., 2011; Marsh et al., 2008). However, several candidates genes have been referred to antisocial personality; until September 2013 in HUGO Navigator 2.0 (An integrated, searchable knowledge base of genetic associations and human genome epidemiology), reported data for OXT and OXTR show their participation with a relatively marginal effect for the genetics associations studies (Wei Yu, 2013). Table 2. Nevertheless, the participation of the OXTR gene shows a pleiotropic effect that could suggest molecular regulation or modulation in the expression of phenotype, which contributes to evaluate the clinical dimension in psychopathy.

Table 2.

Rank	Score Gene	Candidate Gene	Gene information	Genetic Association Studies
1	2.187	MAOA	monoamine oxidase A	31
2	0.651	SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	17
3	0.577	ROBO2	roundabout, axon guidance receptor,	2
4	0.538	DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	1
5	0.383	DRD2	dopamine receptor D2	10
6	0.345	COMT	catechol-O-methyltransferase	9
7	0.23	SLC6A3	solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	6
8	0.153	ALDH2	aldehyde dehydrogenase 2 family	4
9	0.153	HTR1B	5-hydroxytryptamine (serotonin) receptor 1B	4
10	0.153	HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	4
11	0.077	DRD4	dopamine receptor D4	2
12	0.077	DRD5	dopamine receptor D5	2
13	0.077	ANKK1	ankyrin repeat and kinase domain containing 1	2
14	0.077	TPH1	tryptophan hydroxylase 1	2
15	0.038	CHRM2	cholinergic receptor, muscarinic 2	1
16	0.038	CHRNA2	cholinergic receptor, nicotinic, alpha 2 (neuronal)	1
17	0.038	ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	1
18	0.038	CNR1	cannabinoid receptor 1 (brain)	1
19	0.038	DBH	dopamine beta-hydroxylase (dopamine beta-monoxygenase)	1
20	0.038	DRD3	dopamine receptor D3	1
21	0.038	ESR1	estrogen receptor 1	1
30	0.038	OPRM1	opioid receptor, mu 1	1
31	0.038	OXTR	oxytocin receptor	1
35	0.038	SNAP25	synaptosomal-associated protein, 25kDa	1

Genes were ranked according to the published evidence so far of each one of the genes using the algorithm created by Wei Yu and Collaborators (Wei Yu, 2013) .

The neurobiological way that helps us to infer the participation of the OXT system in the modulation of the serotonergic and dopaminergic systems that participate directly in personality disorders is still complex. Currently, we can describe genes or molecules of reference that could refine the molecular networks to infer the expression of patterns set that are typically in the aggressive and antisocial behavior. Even though psychopathy has more literature regarding the androgens and their implications in personality, it is interesting to review the OXT system and the relation with the bioavailability of estrogens, which have been previously associated with the expression of aggressive behaviors.

Over 20 years ago, Caldwell and collaborators (1989) determined how estrogens that are frequently involved in plasticity and synaptogenesis increase the mRNA levels in the lateral preoptic area, which could

explain the reproductive behavior, so the social bond as well. Additionally, Estrogen receptor beta (ERb) in the raphe nuclei, which have as function the serotonin release (5-HT) in the brain, have been identified. Besides, it has been reported their contribution with a greater density of the serotonin receptors 2A (5-HT2A) (Stahl, 2001), which is one of the receptors more associated with the impulsive behavior. Also, estrogens can decrease the expression of the monoamine oxidase A (MAOA), which is one of the candidate genes with best experimental relation to antisocial behaviour (Caspi et al., 2002; S. Y. Lee, Chen, Chang, & Lu, 2013; Wei Yu, 2013).

With these findings, analyzing the contribution of the OXT system and how it could influence in the expression of other genes that were associated with psychopathy could be useful to find a differential expression pattern that can modulate the clinical

spectrum in psychopathy. This assertion is in accordance with the theory of Belsky, which affirms that the increase of susceptibility when developing a psychopathology can be related to polymorphic variations of the OXTR gene (Belsky, 1997). This explanation, has been supported by numerous findings that associate genetic polymorphism with the social pattern expression that have evolved in humans to favor efficient strategies of cooperation, empathy, and moral behavior, which is a constitutive base to differentiate clinical features related to mental and personality disorders (Cacioppo, Cacioppo, & Boomsma, 2013). A way to analyze the OXTR gene and the polymorphisms associated to this gene to increase or decrease the functional expression of the serotonergic network could allow to describe a path to delve into the findings about child abuse by Caspi and collaborators, which determined that individuals who show the genotype for low activity in the MAOA enzyme had more probabilities of developing psychopathy (5-HT levels are regulated by the action of monoamine oxidase, MAO) (Caspi, et al., 2002; Malik, et al., 2012).

Additionally, it is interesting the relation between the 5-HT system and OXT for antisocial and aggressive behavior, several candidate genes that predominate in the serotonergic network (SLC6A4, HTR2A, HTR1B, HTR3A, HTR3B, HTR2C) are involved in psychopathy (Wei Yu, 2013), and the OXT system influences physiologically in the hormonal regulation in the hypothalamic- pituitary- adrenal and neurophysiologically in the bioavailability of serotonin.

6. OXTR AS A POTENTIAL ENDOPHENOTYPE

Endophenotypes are constituted as a quantitative pattern of disadvantage, vulnerability, susceptibility or risk of showing a particular phenotype that can contribute directly to the probability of developing a particular syndrome or pathology (J. M. C. Arias, & C. A. P. Acosta, 2011). At the beginning, the endophenotype concept was coined by Dr. Irving Gottesman to explain the presence of an intermediate phenotype or vulnerability marker (clinical, biochemical, neurophysiological, genetic or cognitive) that is relatively stable in the expression of a specific psychopathological pattern (Gottesman & Gould, 2003).

OXTR has a crucial role in the expression of critical traits strongly associated with psychopathy. Perhaps, the more important one in its diagnosis is impulsivity, and its pathophysiological correlative is in accordance with the aforementioned candidate genes. Impulsivity entails aggressive behaviors, affiliation and prosocial difficulties, and lack of empathy. Currently, it

has been reported that OXTR participates in the regulation of receptors in HTR2A, which have been associated with impulse control changes and aggressive behavior (Zalsman et al., 2011).

In the other hand, OXTR comply with the criteria for heritability, stability and replicability that should have an endophenotype, which suggests that OXTR can be considered as an intermediate molecular phenotype that predominates or interacts in a relevant way in the neurobiology and the etiopathogeny of psychopathy: there is evidence of molecular expression with OXTR in this disorder. Although OXT levels are variable between genders, they establish a relatively stable biomolecular pattern modulating the expression of the most bizarre clinical patterns that are closely linked to psychopathy and impulsivity.

At this moment, more research is needed. There are not yet clear studies to assess if the changes in OXTR cosegregate with this disruptive pattern. However, we may infer that OXTR polymorphisms can modulate a biochemical and genetic network associated with typical psychopathy characteristics, especially those that show lack of empathy, moral construct deficits and increased impulsivity. Furthermore, although the oxytocin effect has been frequently associated with prosocial and altruistic behaviors, there are others (such as the altruistic punishment practiced in social contexts and clung to human cooperation in cooperative patterns searching) that display aggressive behaviors and negative emotions in social competence.

Summarizing, it might be necessary to remodel a gene network that incorporates the functional load of the OXTR gene from its implications in genetic architecture of neural systems. Currently, there are few findings that allow discriminating how a specific polymorphism in the OXTR gene affects positively or negatively the expression or interacts directly with the molecular dynamic of other genes involved in antisocial behavior. It is possible that a best approach to the impact of the OXT system requires refining more dimensional diagnosis methods in psychopathology, analyzing putative molecular networks that could modulate the transcriptional efficiency of genetic polymorphisms reported, and incorporating methods of systems biology that allow refining epistatic processes into a molecular level underlying the differential expression of the phenotype of interest.

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