THE EVOLUTIONARY APPROACH TO CANNABINOID RECEPTORS STRUCTURE

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INTRODUCTION

The endogenous cannabinoids (ECB) system, is comprised of anandamide (AEA), 2-arachdonoylglycerol (2-AG), (Figure 1), endocannabinoid receptors (CNR1 and CNR2) and synthesizing/degrading enzymes. The reports regarding the therapeutic effect of endocannabinoids are sometimes controversial. The reason for this problem might lay in the structural and functional ECB differences in different models and organisms studied.

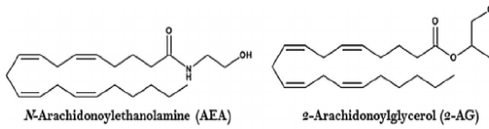

Figure 1. Endogenous cannabinoids (Fonesca, B.M., et al., 2013)

OBJECTIVE

To evaluate our recently published data on the cDNA composition of ECBs in baboons (Rodriquez-Sanchez et al., 2016) and compare it to known functional and structural variants (from genotype to genotype to phenotype) in humans (*Homo sapiens*) and to described phenotypes in the baboons (*Papio spp*), from phenotype to phenotype.

MATERIALS & METHODS

Tissues (liver) were collected during necropsies from animals undergoing pathological examination at the Southwest National Primate Research Center, Texas Biomedical Research Institute (San Antonio, TX, USA). Total RNA was extracted from the tissue samples using TRIZOL reagent according to the manufacturer's instructions. The sequences obtained were translated using the Transeq online program and aligned with human orthologous human gene [GenBank: CNR1 ID: 1268; CNR2 ID: 1269] using the CLUSTAL W program. Naturally occurring mutations are listed on the Human Gene Mutation Database (HGMD): http://www.hgmd.org. Homology table information gathered from Ensembl database: http://useast.ensembl.org/index.html.

RESULTS

CANNABINOID RECEPTOR 1

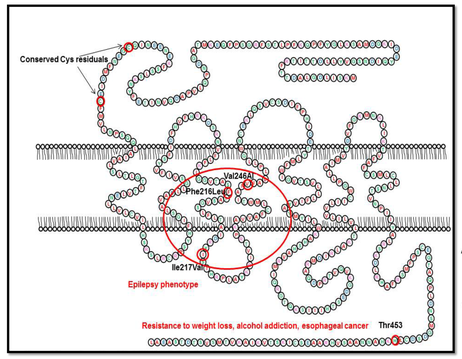

Figure 2. The *CNR1* gene homology between humans (*Homo sapiens*) and baboons (*Papio spp*.) is 98%, not shown, whereas the protein (CB1R) homology is has 100%. Small Red circles are known gene variants in humans with corresponding phenotypes.

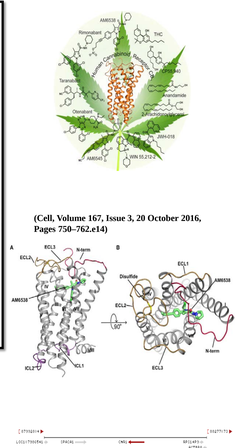

Figure 3. *CNR1* Chromosomal location diagram.

Homology % to humans (protein)	Protein change	Location of amino acid change	Known mutations in humans	Known clinical phenotype and/or function	Reference
100%	-	3' UTR	4895 C/T (rs806368)	Pre eclampsia Decreased Bone Density	Bienertova-Vasku, J., et al., 2011
	-	-	-Allele GG (rs806381), -Allele GG, (rs10485170), -Allele GT (rs6454674)	Increased Non-alcoholic Fatty Liver Disease in PCOS patients	Kulicikowska Plaksej, J., et al.,2014
	-	-	-Allele GG (rs1049353) -1359 G/A	-Increased response to SSRI therapy. -Resistance to weight loss	-Mrijans, M., et al., 2012 -Jaeger, P., et al., 2008
	-T435T -A1359A	-	(rs1049353)	-Lack of metabolic improvement after weight loss with low fat and low carbohydrate diet. -Increased Microvascular complications, diabetic nephropathy/retinopathy	-de Luis, D.A., et al., 2013 -Antonio de Luis, D.,2012 -Buraczynska, M., et al., 2014
	L133I	-	524C>A (rs41311993)	-associated with bipolar disorder	-Minocci, D., et al., 2011
	-	-	-G1359 A in codón 453	-Esophageal cáncer and reduced survival time	-Bedoya, F., et al., 2009
	-	-	1359 G/A (rs1049353)	Drug abusing schizophrenia, neuro-psychiatric disorders	-Aberle, J., et al., 2007 -Monteleone, P., et al., 2010
	-	-	(AAT)12 repeat allele	Cocaine addiction in African-Caribean population	Ballon, N., et al., 2006
	-	-	AATn=12 repeat	Reduced working memory	Alejandra E. Ruiz-Contreras., 2013
	-	-	14 repeat allele (AAT)	Binging/purging anorexia nervosa	Siegfried, Z., et al.,
	-	-	13 repeat allele (AAT)	Restricting Anorexia nervosa	Ando, T., et al., 2014
	-	5' end	-AATn>10 repeat allele	Increased incidence of Inflammatory Bowel Disease	Jiang, Y., et al., 2014
	-	-	-High expression of CB1 receptor	Mantle cell lymphoma	Wasik, A.M., et al., 2014
	-	coding region	-3813A/G (rs1049353)	Obesity	Russo, P., et al., 2007
	-	cytoplasmic tail	1256C>A (A419E, rs1049353)	Signaling and obesity likely associated with protein desensitization	Müller, T.D., et al., 2007
	-	5' UTR	allele A/C (rs754387)	Cannabis and alcohol dependence	Agrawal, A., et al., 2009
	-	5' UTR	allele A/C (rs78074274) CC (rs806377) GG (rs806380)	Increased gaze upon happy faces	Chakrabarti, B., et al., 2011
	-	intron 2	allele AT (rs806379) rs1535255	Associated with obesity	Müller, T.D., et al., 2007
	-	intron 2	alleleA/G (rs806379	Cannabis dependence	Agrawal, A., et al., 2009
	-	exon 3	rs2023239	Increased risk for polysubstance abuse in European and African-Americans	Agrawal, A., et al., 2009
	-	intron 3	rs806370	Associated with obesity	Müller, T.D., et al., 2007

Table 1. Table of clinically relevant CNR1 mutations in the human population.

CANNABINOID RECEPTOR 2

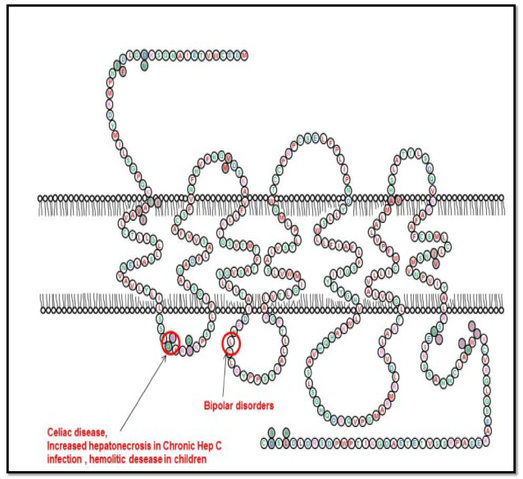

Figure 4. The *CRN2* gene homology between humans (*Homo sapiens)* and baboon (*Papio spp*.) is 95%, whereas the protein (CB2R) homology is 96%. Red circles are known gene variants in humans with corresponding phenotypes; the amino-acid residues which differ from human are presented in black circles adjacent to the in line amino acid sequence.

Homology % to humans (protein)	Protein change	Location of amino acid change	Known mutations in humans	Known clinical phenotype and/or function	Reference
96%	D15N, S19F	First extracellular	524A > C (Leu133Ile) polymorphism (rs41311993)	Bipolar disorder	Minocci, D., et al., 2011
	T34I, V36I.	First helical	188-189 GG/GG homozygotes	Autoimmune diseases	Sipe, J.C., et al., 2005
	-	First Cellular	Codon 63 QQ variant (rs35761398)	Increased hepatonecrosis in Chronic Hep C infection	Coppola, N., et al., 2014
	-	Fourth transmembrane region	-Non-AA Allele -G allele carriers (rs2501431)	Decreased response to SSRI therapy.	-Onaivi, E.S.,et al., 2008 -Mrijans, M., et al., 2012
	Q63R, R66Q	First Cellular	Codon 63 Q>R rs35761398 (CAA/CGG)	Celiac disease	Rossi, F., et al., 2012
	Q63R	second exon	C/T and T/T (rs2501432)	Protective effect against schizophrenia particularly in males	Tong, D., et al.,2013
	H316Y	second exon	C/T allele (rs2229579)	Risk factor for schizophrenia	Tong, D.,et al., 2013
	-	A/C/T	(rs2229579)	Risk for osteoporosis	Woo, J., et al., 2015
	-	-	AA genotype of (rs3003336 and rs4237)	Lower lumbar spine BMD	Woo, J.H., et al., 2015
	-	-	A>G (rs16829926)	No association in Korean women with BMD	Woo, J.H., et al., 2015
	-	-	allele A/G (rs3123554)	Associated with lower BMI	Ketterer, C., et al., 2014

Table 2. Table of clinically relevant CNR2 mutations in the human population.

Figure 5. CNR2 Chromosomal location diagram.

RESULTS

Among the members of the ECB family, the CNR1 was the most conserved gene between humans and baboons with 98% homology and 100% protein homology (Figure 2). The CNR2 gene has a homology of 95% with humans and the protein has a 96% homology (Figure 4). The phenotypes, associated with the mutations of the untranslated regions of this gene in humans are not described in the baboons. In contrast, one of the differences in the CNR2 structure was detected in the only clinically known region showing the relevant polymorphism in the human receptor. Phenotypes associated with this polymorphism are not described in the baboons (Figure 4). Clinically relevant mutations in CNR1 and CNR2 are shown in table 1 and 2. A diagram of CNR2 gene is shown in Figure 5.

CONCLUSION

The presented data provides important information for translational and pharmacological studies of substance of abuse in non-human primate model and evolutionary understanding of human disorders.

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