Published in final edited form as:
Neurosci Lett. 2008 August 8; 440(3): 280–283.

Genetic variants in the cocaine- and amphetamine-regulated transcript gene (*CARTPT*) and cocaine dependence

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Abstract

Dopaminergic brain systems have been implicated to play a major role in drug reward, thus making genes involved in these circuits plausible candidates for susceptibility to substance use disorders. The cocaine- and amphetamine-regulated transcript peptide (CARTPT) is involved in reward and feeding behavior and has functional characteristics of an endogenous psychostimulant. In this study we tested the hypothesis that variation in the *CARTPT* gene increases susceptibility to cocaine dependence in individuals of African descent. Genotypes of three HapMap tagging SNPs (rs6894758; rs11575893; rs17358300) across the *CARTPT* gene region were obtained in cocaine dependent individuals (n=348) and normal controls (n=256). All subjects were of African descent. There were no significant differences in allele, genotype or haplotype frequencies between cases and controls for any of the tested SNPs. Our results do not support an association of the *CARTPT* gene with cocaine dependence; however, additional studies using larger samples, comprehensive SNP coverage, and different populations are necessary to conclusively rule out *CARTPT* as a contributing factor in the etiology of cocaine dependence.

Keywords

genetics; association study; haplotype; addiction; substance abuse; cocaine

Introduction

Genetic studies estimate that 65−78% of the vulnerability risk for cocaine dependence is heritable [24,25]; however, identification of genetic susceptibility factors has been difficult

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Conflict of Interest Statement / Disclosure
The authors report no biomedical financial interests or potential conflicts of interest.

due to the complex mode of inheritance and clinical heterogeneity. Dopaminergic brain systems have been implicated to play a major role in drug reward [21], thus making genes involved in these circuits plausible candidates for influencing susceptibility to substance use disorders. In fact, several genes coding for the dopaminergic system have been investigated in cocaine dependence including genes for the dopamine receptor D2 (DRD2) [15,31,33,36] the dopamine receptor D3 (DRD3) [6,13,31], the dopamine receptor D4 (DRD4) [4] and the dopamine transporter (DAT) [16,17,37]. The results of all these studies have been conflicting with some positive reports and some negative findings, possibly due to small sample sizes and the complex genetic nature of cocaine dependence.

The cocaine- and amphetamine-regulated transcript (CART) is a novel neuropeptide thought be involved in reward and feeding behaviors [11,22,27]. Several lines of evidence suggest a role of the CART peptide in the actions of psychostimulant drugs of abuse. CARTPT is predominately expressed in target regions of the mesocorticolimbic dopamine system, such as the nucleus accumbens, amygdala and orbitofrontal cortex [10,20]. Experiments in rats show that CART mRNA expression is upregulated after acute cocaine self administration in these brain regions [8]; however, the results remain controversial since others have failed to replicated these findings [29,44] and perhaps a binge-dosing regimen might be required to consistently increase CART expression following cocaine exposure [5,12,19]. Interestingly, this dosing regimen reflects closer the use of cocaine in humans and in fact postmortem brain studies of cocaine users demonstrate increased levels of CART mRNA [1,42].

Genetic variation in the gene encoding the CART peptide (*CARTPT*) might influence expression and/or function of the peptide, which might have an effect on the degree of the rewarding and reinforcing properties of cocaine. In this study, we tested the hypothesis that variation in the *CARTPT* gene increases susceptibility to cocaine dependence in individuals of African descent.

Materials and methods

DNA samples from cocaine dependent individuals of African descent (n=348; 72% males, mean age: 43) were collected during clinical studies of cocaine dependence at the University of Pennsylvania Treatment Research Center. Subjects were at least 18 years of age and were all assessed with the Structured Clinical Interview for DSM Disorders (SCID) and urine drug screens were obtained. All patients had a clinical diagnosis of cocaine dependence as defined by DSM-IV. Exclusion criteria were all psychiatric axis I disorders except alcohol dependence/abuse and nicotine dependence. Family history was not obtained and ethnicity was determined by self report. Confidentiality of the participants' clinical data and genetic data was ensured by using a dual coding system that provides a “firewall” mechanism between the identifier on the DNA and clinical data. Control samples from individuals of African descent (n=256; 29% males, mean age: 40) were collected at the University of Pennsylvania, Thomas Jefferson University and through the National Institute of Mental Health Genetics Initiative (www.nimhgenetics.org). Control individuals had no history of substance use disorders or other psychiatric illness as determined by semi-structured interviews. Control subjects were not assessed with a urine drug screen and ethnicity determination was by self-report. Peripheral blood samples were obtained and genomic DNA was extracted from peripheral leukocytes by standard procedures. All protocols were approved by the Institutional Review Boards and written informed consent was obtained for all participating individuals.

The *CARTPT* gene contains 3 exons and spans 1879 bp (NCBI accession NM_004291). SNPs for genotyping were selected using the tagging SNP algorithm based on available HapMap data with a minor allele frequency (MAF) greater then 0.15 in Yoruban population and a pairwise linkage disequilibrium (LD) r^2 cutoff of >0.8 (SNP1: rs6894758; SNP2: rs11575893;

SNP3: rs17358300). Genotyping of these three HapMap tagging SNPs across the *CARTPT* gene region was performed using the Applied Biosystems Inc. (ABI) "Assays-on-demand" (ABI, Foster City, CA, USA) SNP genotyping assay as per manufacturers protocol. This genotyping method uses TaqMan technology and a real-time sequence detection system. Briefly, two primers and an internal labeled TaqMan probe are combined with the 5'−3' nuclease activity of *Taq* DNA polymerase. During the PCR reaction a fluorescent reporter is released only when probe hybridization and amplification of the target sequence have occurred. Measurement of this fluorescence intensity offers a sensitive method to determine the presence or absence of specific sequences. Reactions were performed in 5 μl volumes and contained 2 ng DNA, 1x Taqman Universal Mastermix (Applied Biosystems), 200 nM of each probe and 900 nM of each primer. Thermal cycler conditions were as follows: 10 min at 95 °C and 40 cycles of 15 sec at 95°C and 1 min at 60°C. End-point fluorescence was measured after cycling. Alleles were assigned using SDS 2.1 software (Applied Biosystems). Genotyping success rates were between 98.8 and 99.5%. Genotyping quality was confirmed by genotyping 10% duplicates for cases and controls. Concordance rates of genotypes were 99.8%. Genotypes and allele frequencies were compared between groups using Chi square contingency analysis. A two-tailed type I error rate of 5% was chosen for the analysis. LD between markers and haplotypes were estimated using the COCAPHASE program [9].

Results

There were no significant differences in allele, genotype or haplotype frequencies between cases and controls for any of the tested SNPs (Table 1). Hardy-Weinberg equilibrium (HWE) was calculated separately for cases and controls and no significant deviation was observed for any of the markers (rs6894758: cases p=0.229, controls p=0.803; rs11575893: cases p=0.098, controls p=0.235; rs17358300: cases p=0.601, controls p=0.928). Allele frequencies were similar to those published in the HapMap database for Yoruba in Ibadan, Nigeria. There was low to moderate LD between markers: D'=1 between all SNPs and r^2 ranging from 0.11 to 0.47 between markers. Power to detect an effect size of 1.5 was moderate to good (0.78−0.86) as estimated by the Quanto program [14].

Discussion

Our study failed to observe a statistically significant association for any of the genotyped SNPs in the *CARTPT* gene and cocaine dependence. Haplotype analysis also failed to show any significant association with disease. These results provide no support for the possibility that polymorphisms in *CARTPT* play a major role in susceptibility to cocaine dependence; however, our study has limitations which must be carefully considered before excluding *CARTPT* as a candidate gene for cocaine dependence.

The sample size used in this study was reasonably powered to detect risk alleles of major effect size, but we had limited power to detect risk alleles of small effects which could explain our negative results. Sample sizes in the thousands are necessary to detect risk alleles of small effects. On the other hand this increase in sample size might bring an increase in genetic heterogeneity and might contribute to undetected population stratification influencing outcomes of association analyses [28]. Undetected differences in population structure can mimic the signal of association and lead to false positive results or real effects that are missed [39]. This is a particular concern for analyses of samples of African-American descent, since recent studies indicate larger genetic admixture than previously thought [35,38,43,47]. Possible ways to control for these stratification issues are the use of genomic controls [3,7] and/or the use of a family-based association design, a strategy that matches the genotype of an affected offspring with parental alleles not inherited by the offspring [41]. Ultimately, replication

studies and additional studies in different population are necessary to comprehensively evaluate CARTPT in cocaine dependence.

Besides these potential issues of genetic heterogeneity and population stratification, it is also important to consider limitations of clinical heterogeneity. All patients were diagnosed according to DSM-IV criteria and the diagnosis of cocaine dependence was confirmed using a urine drug screen; however, comorbid substance use of alcohol and nicotine might have differed between patients. In addition, the control subjects were assessed using semi-structured interviews but did not undergo urine drug testing. While drug testing is useful in establishing a diagnosis, it might not be useful for assessment of controls since it does not rule out past exposure or substance use. Unreported or minimized substance abuse in the control population is thus an important limitation that needs to be considered; however, even under the assumption that the prevalence of cocaine addiction of 0.5−1% was present in our control group, this factor might have only a minor influence when comparing the control group to the group of cocaine cases.

Another potential reason why we failed to detect an association in this study could be related to the LD structure of the gene. Our results indicate low to moderate LD between the markers, thus limiting the ability to conclusively rule out other variation which might play a relevant role. The low LD between markers is surprising, given the close proximity of the SNPs in this very small gene (1879bp). Comparison of the LD structure of available HapMap data for Caucasians, Chinese, Japanese and Yorubin populations confirms low LD across populations. This might indicate the phenomenon of gene conversion [2] and high genetic recombination rates (“recombination hotspot”). Homologous recombination hotspots are DNA sites exhibiting increased frequency of recombination and may be regulated primarily by discrete DNA sites and proteins that interact with those sites [45]. Recent studies revealed that recombination hotspots are a common feature of the human genome [30,32] and contribute to the block-like pattern of haplotypes [18]. Characterization and understanding of the molecular mechanisms of these hotspots is of critical importance for designing better strategies in association studies of complex diseases [23,26,34,40,46]. Our results indicate that the *CARTPT* gene falls into one of these hotspots and no information is available on the biological relevance of this complex genomic structure. The complexity of the small genomic region of the *CARTPT* gene might require large scale sequencing of cases and controls in order to detect rare variations affecting illness and to evaluate this genomic region comprehensively.

In summary, our results do not support an association of the *CARTPT* gene with cocaine dependence; however, additional studies using larger samples, comprehensive SNP coverage, and different populations are necessary to conclusively rule out CARTPT as a contributing factor in the etiology of cocaine dependence.

Acknowledgements

This work was supported by the Center for Neurobiology and Behavior, Department of Psychiatry, University of Pennsylvania. Financial support is gratefully acknowledged from National Institutes of Health grants MH59553, MH63876 (W.H.B.), T32MH014654-29A1 (F.W.L.), NIDA grants P60-051186 (C.P.O.) and P50-12756 (H.M.P), the VISN4 Mental Illness Research and Clinical Center grant from the Veterans Affairs Administration (D.W.O.), grants from the National Alliance for Research on Schizophrenia and Depression (W.H.B. and F.W.L.), a grant from the Tzedakah Foundation (W.H.B.), the Daland Fellowship Award by the American Philosophical Society (F.W.L.), the McCabe Foundation (to F.W.L) and the APIRE/AstraZeneca Young Minds in Psychiatry Award (to F.W.L.) and a grant from Philip and Marcia Cohen (W.H.B.). We thank Candice Schwebel for technical assistance. Most importantly, we thank the subjects who have participated in and contributed to these studies.

The NIMH control subjects were collected by the NIMH Schizophrenia Genetics Initiative 'Molecular Genetics of Schizophrenia II' (MGS-2) collaboration. The investigators and coinvestigators are: ENH/Northwestern University, Evanston, IL, MH059571 – Pablo V. Gejman, MD (Collaboration Coordinator; PI), Alan R. Sanders, MD; Emory University School of Medicine, Atlanta, GA, MH59587 – Farooq Amin, MD (PI); Louisiana State University Health Sciences Center; New Orleans, LA, MH067257 – Nancy Buccola APRN, BC, MSN (PI); University of California-

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Table 1

Genotype and Allele Frequencies of Variations in the *CARTPT* Gene in Cases and Controls

SNP	Sample	n	Genotype frequency			P^{*a}	Allele frequency	P^{*b}
rs6894758			T/T	T/C	C/C		f(T)	
	Cocaine	348	0.405	0.486	0.109	0.705	0.648	0.561
	Controls	256	0.438	0.453	0.109		0.664	
rs11575893			C/C	C/T	T/T		f(C)	
	Cocaine	344	0.610	0.360	0.029	0.891	0.791	0.693
	Controls	256	0.598	0.367	0.035		0.781	
rs17358300			C/C	C/T	T/T		f(C)	
	Cocaine	346	0.497	0.408	0.095	0.881	0.701	0.670
	Controls	256	0.477	0.426	0.098		0.689	

* type-I error rates for comparison of genotype[a] and allele[b] frequencies between cocaine dependent individuals and controls.