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Research Article

The Dopamine Receptor D1(DRD1) as Target for Developinga Therapy for Cocaine Addiction

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Abstract

It takes approximately fifteen years and nearly one billion dollars to bring a drug to market. A computational approach shows promise in being used to find therapeutics in less time and cost-effectively [1]. The approach reported herein mines publicly available gene expression data to uncover a gene is up or down regulated from microarray experiments and may lead to the repurposing of a current Food and Drug Administration (FDA)-approved drug to help cure cocaine addiction. Publicly available data from National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) repository (https://www.ncbi.nlm.nih.gov/geo/) was used. Data sets were downloaded to uncover the gene expression difference between saline and cocaine-treated rats and the top genes analyzed. The secondary analysis included the correlation with FDA-approved drug gene expression data found on the Broad Institute's Connectivity Map (CMap: https://clue.io/cmap) website. This resulted in the identification of compounds that antagonize the dopamine receptor D1(DRD1).

Keywords: Connectivity Map, DRD1, Cocaine, Loxpine, Olanzapine, Clozapine, Gene Expression

Abbreviations: NAcc: Nucleus Accumbency; DRD1: Dopamine Receptor Type 1; PFC: Prefrontal Cortex

Introduction

Cocaine is a crystalline tropane alkaloid that blocks the Dopamine (DA), norepinephrine, and serotonin reuptake transporters (DAT, NET, and SERT). Cocaine's addictive properties are ascribed to the DA reward system and because it blocks the DAT, it generates higher than normal concentrations of DA in the synapse and causes euphoria [2]. Cocaine addiction, a global health problem, warrants the development of behavioral therapies and medication(s). The purpose of this study is to discover a cocaine replacement treatment that can be used with behavioral therapies. It is hypothesized that relationships can be predicted between drugs and disease by comparing gene expression data of healthy and addicted subjects and correlate the differences with gene expression data from FDA-approved drugs. These predictions should give rise to potential therapeutics based on this correlation. The DRD1 is the most abundant dopamine receptor subtype in the central nervous system. It is a G-protein coupled receptor that stimulates adenylyl cyclase and activates cyclic AMP-dependent

protein kinases. DRD1 regulates neuronal growth and development, mediates specific behavioral responses, and modulates dopamine receptor D2-mediated events. DRD1 is involved in cocaine's reward mechanism and even an acute amount causes DRD1 to be activated [3-5].

Methods

The datasets (GDS 255 and 1608) [6] were accessed from the NCBI GEO site (https://www.ncbi.nlm.nih.gov/geo/). GEO2R analyses were conducted for the GDS255 (n=10) & GDS1608 (n=63) datasets, respectively, using the following parameters to compare the difference in gene expression of rat brain tissue from the Nucleus Accumbens (DA) and Prefrontal Cortex (5-HT): the Benjamin& Hochberg False discovery rate, auto-detected log transformation, and NCBI Platform annotations. A fold-change was regarded as significant with P<0.05. Lima precision weights and force normalization were not applied. The Top 250 Differentially Expressed Genes (DEGs) were further narrowed to the Top 16 DEGs. Each of the Top 16 DEGs were noted as up-regulated or down-regulated. Connectivity Map [7] used to uncover potential therapies based on the top genes analyzed at the NCBI GEO site and www.Clinicaltrials.gov was used to determine FDA-approved status of potential therapies.

Results and Discussion

Analysis of GDS 255 and 1608 with GEO2R revealed the top 250 genes impacted by cocaine treatment. Figure 1a and 1b are the volcano plots that show statistical significance (P value) versus magnitude of change (fold change). They depict what may be the most biologically significant genes when comparing the Nucleus Accumbency (NAcc) to the prefrontal cortex PFC in rats (Figure 1). The top 16 genes from the Volcano plot are shown in tabular form (Table 1). DRD1 is evident in the top sixteen most significant genes in both datasets. The Connectivity Map led to correlating drugs that target the DRD1 and provide therapeutic value. A total of 46 drugs were identified from the correlation with the majority (n=20) used for the treatment of schizophrenia. Figure 2 depicts loxapine [8], clozapine [9], and olanzapine [10]; these were chosen for further investigation due to their drug-gene interactions, and low abuse potential (Table 2). The piperazines, also classified as benzodiazepines, act at multiple sites Table 3 [11]. These off-target interactions explain the myriad of side effects individuals experience when taking these treatments. Structurally, it appears that replacing the ring oxygen with a nitrogen drastically reduced the number of side effects. Also, removing the Cl and replacing the benzene with a thiophane did not lead to a better medication (Table 3) [12].

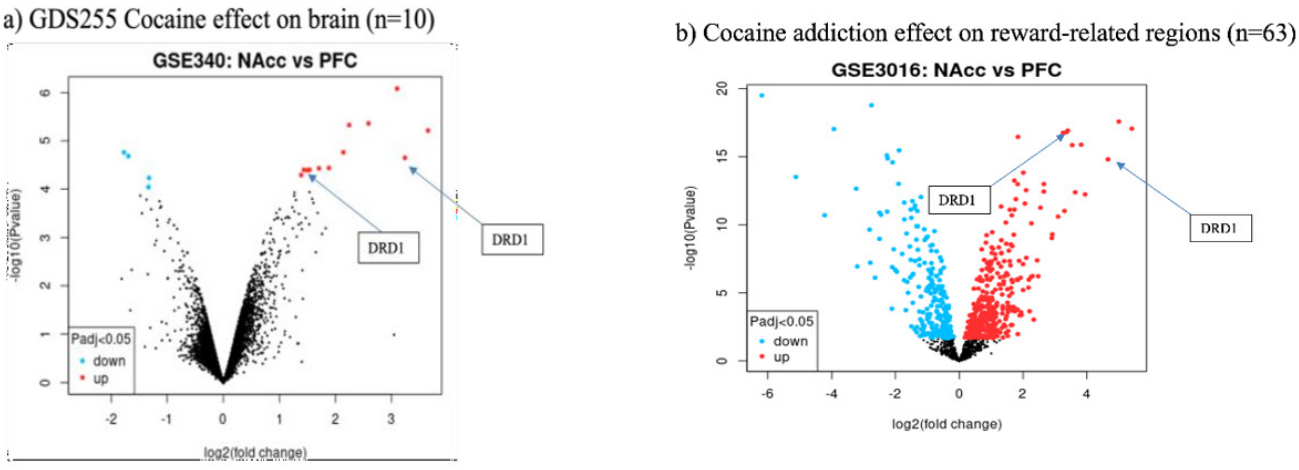


Figure 1: Volcano plots for microarray data generated from treating rats with cocaine.

Table1: Top genes affected when rats are treated with cocaine.

ID	Adj PVal	PValue	t	B	logFC	GeneSymbol	GeneTitle
S49491_s_at	0.0071	8.31E-07	27.37018	4.9047	3.098391	Penk	proenkephalin
S80376_at	0.0131	4.37E-06	19.81912	4.2102	2.588456	Gnal	G protein subunit pha L
U10071_at	0.0131	4.72E-06	19.52226	4.1707	2.242827	Cartpt	CART prepropeptide
M15191_s_at	0.0131	6.15E-06	18.53978	4.0303	3.649552	Tac1	tachykinin, precursor1
U08290_at	0.024	1.73E-05	15.12888	3.4033	2.139718	Nnat	Neurontin
U88958_at	0.024	1.73E-05	-15.1285	3.4032	-1.77131	Nrn1	neuritin1
L09119_at	0.024	2.08E-05	-14.5968	3.2807	-1.69419	Nrgn	neurogranin

S46131mRNA_s_at	0.024	2.25E-05	14.37348	3.2269	3.238845	Drd1	dopaminereceptorD1
M24852_at	0.0268	3.65E-05	13.06267	2.879	1.881498	Pcp4	Purkinje cellprotein4
rc_AI639435_at	0.0268	3.71E-05	13.01835	2.8662	1.7048	Pcp4l1	Purkinje cellprotein4-like1
AF016387_g_at	0.0268	3.98E-05	12.84343	2.815	1.538098	Rxrg	retinoid X receptor gamma
rc_AA859661_at	0.0268	3.98E-05	12.83865	2.8136	1.438066	Qpct	glutaminyl-peptide cycle transferase
M35077_s_at	0.0268	4.08E-05	12.77641	2.7951	1.499709	Drd1	dopaminereceptorD1
S49400_at	0.0312	5.11E-05	12.21747	2.6219	1.388096	Ptpn5	protein tyrosine phosphatase, non-receptortype5
X01032_at	0.0334	5.87E-05	-11.887	2.5135	-1.32667	Cck	cholecystokinin
rc_AI175539_at	0.0484	9.07E-05	-10.899	2.1594	-1.33401	Pvalb	parvalbumin

a. GDS255 Cocaine Effecton Brain (n=10).

ID	AdjPVal	PValue	t	B	logFC	GeneSymbol	GeneTitle
M60654_at	4.14E-17	3.13E-20	-34.2603	36.27588	-6.18865	Adra1d	adrenoceptoralpha1D
D12519_s_at	1.09E-16	1.65E-19	-31.6604	34.70325	-2.74987	Stx1a	syntaxin1A
X56065_s_at	1.14E-15	2.59E-18	27.76732	32.05391	5.002317	Drd2	dopaminereceptorD2
L13040_s_at	2.43E-15	8.67E-18	26.20541	30.87473	5.409158	Calcr	Calcitonin receptor
rc_AI228113_s_at	2.43E-15	9.19E-18	-26.1319	30.81742	-3.92898	Nptxr	Neuronal pentraxin receptor
X56306_s_at	2.66E-15	1.21E-17	25.79265	30.55057	3.402464	Tac1	tachykinin, precursor1
S46131mRNA_s_at	2.88E-15	1.62E-17	25.43094	30.26195	3.350796	Drd1	dopaminereceptorD1
S49491_s_at	2.88E-15	1.74E-17	25.34278	30.19096	3.252765	Penk	proenkephalin
AF030253_at	5.14E-15	3.50E-17	24.50584	29.50375	1.839249	Slc32a1	solutecarrierfamily32 member1
AJ002942cds_at	1.70E-14	1.31E-16	22.99198	28.19661	3.819628	Rarb	retinoic acid receptor, beta
S47609_s_at	1.70E-14	1.41E-16	22.90942	28.1228	3.541166	Adora2a	adenosine A2areceptor
L09119_g_at	3.79E-14	3.44E-16	-21.9413	27.23673	-1.88664	Nrgn	neurogranin
AF058795_at	8.22E-14	8.08E-16	-21.0488	26.38438	-2.26837	Gabbr2	gamma-aminobutyric acid type Breceptorsubunit2
L09119_at	1.27E-13	1.35E-15	-20.5309	25.87323	-2.24395	Nrgn	neurogranin
M35077_s_at	1.37E-13	1.56E-15	20.38459	25.72659	4.661511	Drd1	dopaminereceptorD1
U90312_at	2.12E-13	2.57E-15	-19.8915	25.22453	-2.09104	Synj2	synaptojanin2

b. GDS1608 Cocaine addiction effect on reward-related regions (n=63).

Table 2: Current mechanism of action (MoA) and status of drugs.

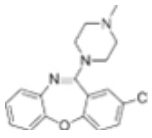
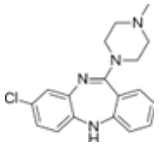
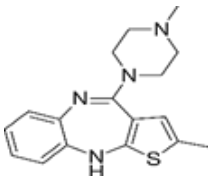
Drug	Structure	MoA	FDA-approval
Loxapine		Receptor antagonist: dopamine, serotonin, norepinephrine, choline, histamine	Schizophrenia
Clozapine		receptor antagonism: dopamine, serotonin, muscarinic	Schizophrenia
Olanzapine		receptor antagonism: dopamine, serotonin, norepinephrine, histamine	Schizophrenia, Bipolar Disorder, Depression

Table 3: Genes impacted by Loxapine, Clozapine and Olanzapine.

Drug	Genes	Side effects
Loxapine	ADRA1A, ADRA1B, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2, ADRB3, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, DRD3, DRD4, DRD5, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, HRH1, HRH2, HRH4, HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR3A, HTR5A, HTR6, HTR7	dizziness, feeling unsteady, or having trouble keeping your balance, faintness, weakness, difficulty falling asleep or staying asleep, blurred vision, dry mouth, increased saliva, nausea, vomiting, constipation, difficulty urinating, excessive thirst, weight gain or loss, agitation, slurred speech, headache, rash, itching, hair loss, flushing, drooping eyelids, puffing of the face, blank facial expression, shuffling walk, unusual, slowed, or uncontrollable movements of any part of the body, restlessness, numbness, burning, or tingling of the hands or feet, breast milk production, breast enlargement, missed menstrual periods, decreased sexual ability in men
Clozapine	ADRA1A, ADRA1B, ADRA1D, ADRA2A, ADRA2B, ADRA2C, CALY, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, DRD3, DRD4, DRD5, HRH1, HRH4, HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR3A, HTR5A, HTR6, HTR7	drowsiness, dizziness, feeling unsteady, or having trouble keeping your balance, increased salivation, dry mouth, restlessness, headache
Olanzapine	ADRA1A, ADRA1B, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2, ADRB3, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, DRD3, DRD4, DRD5, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, HRH1, HRH2, HRH4, HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR3A, HTR5A, HTR6, HTR7	dizziness, feeling unsteady, or having trouble keeping your balance,restlessness,unusualbehavior,depression,difficultyfallingasleeporstaying asleep, weakness, unusual movements of your face or body that you cannot control, falling, sore throat, fever, chills, (and other signs of infection), very stiff muscles, excess sweating, fast or difficulty walking, constipation, weight gain, dry mouth, pain in arms/legs/back/ joints, breast enlargement or discharge, late or missed menstrual periods, decreased sexual skin redness or peeling, hives, difficulty breathing or swallowing

Conclusion

DRD1 is a viable target for reducing cocaine-seeking behavior. Given the information regarding benzodiazepines that interact with this receptor, it appears that clozapine is superior due to the decreased number of side effects. Future Structure-Activity Relationship (SAR) studies may be needed and assist with uncovering a better pharmacotherapy for cocaine addiction.

Conflict of interest

No Conflict of interest.

Acknowledgement

None.

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