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DOPAMINE LEVELS IN THE RETINAS OF COCAINE ADDICTS

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Abstract. Activities that may lead to addiction cause an increase in dopamine in the reward systems of the brain. Dopamine is also released in response to light in the retina. Chronic use of drugs such as cocaine may cause a depletion of dopamine. 9 patients and 11 controls were included in a study to assess dopamine levels in the retinas and, indirectly, levels in the reward systems of cocaine users during withdrawal. Electrooculogram readings were done to measure the potential differences during light and dark adaptation in subjects. The normal 5 mv increase in potential from the cornea to Bruchs membrane, the innermost layer of the choroid, reaches a trough during the dark and a peak during light. Results obtained from troughs partially from peaks in linear regression analyses revealed a trend of decreased light responses in the patient group compared to controls which did not reach statistical significance.

INTRODUCTION

Dopamine is a neurotransmitter and neuromodulator involved in a wide array of functions in the brain including cognition, memory, motivation, reward, eating and sleep as well as in the periphery: vision, movement, cardiovascular tone, hormone regulation and renal function [1]. Dopamine reward systems include the mesolimbic pathway which begins with dopaminergic neurons in the midbrain Ventral Tegmental Area (VTA) that projects to the ventral striatum (nucleus accumbens, olfactory tubercle) and associated limbic structures (hippocampus and amygdala), and the mesocortical pathway which projects from the VTA to the prefrontal and orbitofrontal cortices. [2], [3], [4]. Activation of the reward system from the use of drugs such as alcohol, nicotine and psychostimulants or compulsive behaviors such as pathological gambling and stress induced overeating cause an increase in dopamine [5], [6], [7]. The surge in dopamine in the nucleus accumbens causes immediate euphoria which results in reward and positive reinforcement of drug use or compulsive behaviors. Additional pathways involved in reward and the maintenance of addiction include the nigrostriatal pathway which comprises dopaminergic neurons in the substantia nigra that synapse on the dorsal striatum (caudate and putamen) [4] and the striato-thalamocortical circuit which controls unconscious drives that regulate behaviors geared towards the acquisition and repetitive use of drugs despite diminishing reward and negative consequences.

Disruptions in these circuits on imaging studies have been observed in cocaine users [3]. Dopamine is released from vesicles in presynaptic neurons and binds to postsynaptic receptors D1 (D1, D5) which increase cAMP and D2 receptors (D2, D3, D4) which inhibit or have no effects on cAMP formation. The most important final outcome of activation of dopamine receptors is modulation of glutamate and GABA activity in the brain [1]. Psychostimulant drugs such as cocaine cause acute and chronic changes in the brain which may or may not be permanent. Drug addiction has been associated with major disruptions in circadian rhythms and the sleep/wake cycle. Faulty connections between the Suprachiasmatic Nucleus (SCN), molecular rhythms in the striatum and locomotor activity patterns caused by the administration of psychoactive drugs may contribute to addiction. Melatonin may influence cocaine sensitization and preference through modulation of diurnal rhythms in dopamine transmission in the brain [8]. Cocaine binds to dopamine transporters on presynaptic neurons and blocks reuptake of dopamine thereby flooding postsynaptic receptors with dopamine [9], [10]. Over time, the neurotransmitter molecules present in synapses are metabolized via the enzyme Catechol-O-Methyltransferase (COMT) to the intermediate metabolite 3-methoxytyramine. Synaptic dopamine may be degraded faster than it can be synthesized or resorbed into presynaptic neurons for vesicular storage and subsequent release. Cocaine also inhibits dopamine vesicle binding making the neurotransmitter vulnerable to intracellular metabolism by Monoamine Oxidase B (MAO-B). The increased dopamine metabolism and excretion caused by cocaine put demands on dopamine synthesis which may lead to dopamine deficiency if synthesis of the neurotransmitter is not able to keep up [11]. One

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study revealed upregulation of striatal dopamine transporters in acutely abstinent cocaine abused patients. These findings suggest an attempt to overcome the chronic reuptake blockade by cocaine thereby creating a functional decrease of dopamine at synapses [12]. All these findings suggest that a state of chronic dopamine depletion may contribute to lack of pleasure and depression that may cause negative reinforcement for active craving and behaviors to obtain more cocaine [11]. Dopamine antagonists block self-stimulation in animals by preventing euphoria and attenuating the reinforcing properties of cocaine [11], [13]. Haloperidol, clozapine and Vitamin E but not the dopamine antagonist MK-801 were found to prevent cocaine's effects [14]. However, craving for cocaine in the presence of dopamine antagonists may increase [11]. Dopamine receptor agonists such as bromocriptine and ABT-431, a selective D1 agonist, may alleviate cocaine urges in chronic users [11], [15].

Dopamine is also found in high concentrations in the retinal pigmented epithelium where it is instrumental in color vision and light adaptation. Dopamine is released during light adaptation and in lesser amounts during the dark. Photoreceptors (rods and cones) respond to darkness with depolarization of cell membranes resulting in the release of glutamate. These cell membranes hyperpolarize in the presence of light resulting in decreased release of glutamate [16], [17]. The ultimate effect of glutamate is to decrease dopamine synthesis and release from amacrine cells in the inner plexiform layer of the retina. Dopamine acts on D1 and D2 receptors on a variety of neurons distributed widely throughout the retina. Studies show deficits in signal flow through cone circuits and light adaptation in the presence of dopamine depletion. Cocaine withdrawn patients displayed significantly higher error scores on color vision tests and blue-yellow color vision losses compared to controls on Electroretinogram (ERG) findings [18]. Parkinson's disease patients who have 50% less retinal dopamine showed decreases in ERG blue cone amplitudes [18]. One night of sleep deprivation significantly increased light adaptive RPE potentials on Electrooculogram (EOG) measurements in Parkinson's disease patients [19]. This current study was conducted to determine if patients with cocaine dependence demonstrated lower light adaptation responses or not in the retina due to chronic dopamine deficiency as measured by electrooculogram readings.

MATERIALS AND METHOD

11 controls and 9 patients were recruited from the Long Beach VA Medical Center in Long Beach, CA. Patients were screened based on exclusion and inclusion criteria. Inclusion criteria for subjects included males and females between the ages of 18 and 80 years old, with a history of cocaine dependence and regular use of cocaine in the past 3 months. They needed to be in good overall physical health. Exclusion criteria included (1) chronically severe physical problems including significant myopia, retinal detachment or other eye diseases which limit vision (2) other comorbid Axis I conditions including schizophrenia, schizoaffective disorder, major depressive disorder and PTSD (3) maintenance on psychoactive medications, especially, antipsychotics but, also, antidepressants, anticonvulsants or anxiolytics and (4) heavy use of amphetamines, opiates, alcohol or drugs other than cocaine in the past 3 months. A history of drug use, family drug/ mental illness and past history of psychiatric disorders was obtained.

TABLE 1
CONTROL DEMOGRAPHIC INFORMATION

Age	Race	Gender	Marital Status	Education	Family History
50	W	M	Married	Post Grad	None
51	B	M	Married	Trade Tech	None
57	W	M	Married	College	ETOH
38	W	M	Married	College	- -
57	W	M	Married	College	None
38	W	M	Single	Post Grad	Affective
45	B	M	Single	- -	- -
47	W	F	Single	Post Grad	- -
65	W	M	Single	H.S.	None
56	W	M	Married	Post Grad	None
34	Asian	M	Married	Post Grad	Drug/ETOH

TABLE 2
PATIENT DEMOGRAPHIC INFORMATION

Age	Race	Gender	Marital Status	Education	Family History
42	B	M	Married	H.S.	Drug use
52	B	M	Divorced	Part H.S.	None
59	B	M	Separated	Part college	Drug use
51	W	M	Divorced	Part college	Drug use
51	B	M	Divorced	H.S.	ETOH
43	B	M	Single	H.S.	ETOH/drug
43	W	M	Divorced	H.S.	- -
44	B	M	Single	Trade Tech	Affect/ETOH
44	B	M	Divorced	H.S.	Affect/ETOH

Rating scales including the Hamilton Depression Rating Scale (17 questions), Hamilton Anxiety Scale and Bech-Rafaelsen Mania Scale were obtained for each subject. Subjects were exposed to darkness for 15 minutes and then to illumination with 1200 lux for another 15 minutes. Each test subject lay on a hospital bed placed a set distance below a group of fluorescent lights. LED lights were placed on a diffusing element over the fluorescent lights. Excess movement was limited by placing the subjects' heads in a padded wooden headrest.

Individuals were then asked to look alternately at two Light Emitting Diodes (LEDs) which flashed sequentially every three seconds. The LEDs were placed 74 degrees apart in the visual field. Output signals from silver-silver chloride cup electrodes placed near the canthal region of one eye with a reference electrode over a mastoid area were transmitted to a Grass amplifier, attenuated through a low pass filter (15 Hz) and recorded.

Corneofundal potentials as measured from extraocular movements were recorded at 1 minute intervals and averaged during exposure to darkness and then light. For data analyses, peak and trough amplitudes were computed from the time readings by a least squares fit to a generalized peak function (asymmetric double sigmoidal curve with a floating baseline: PeakFit, Jandel Scientific).

RESULTS

See Table 1. Mean age of the controls was 48.9 yrs (SD=9.62, SEM=2.90). See Table 2. Mean age of patients was 47.6 yrs (SD=5.83, SEM=1.94). The patient group was slightly more depressed than the controls, but there was no significant difference between the two groups. Means (SD) of rating scales for the patients were HAM-D (17) = 6.54 (3.64); HAM-A = 5.44 (3.5); BR Mania = 0.22 (4.29); SOMA = 12.89 (6.66). In Figures 1 and 2, light response values were calculated by performing linear regressions and partialling the effects of the troughs from the peaks to remove the effects of glutamate during dark phases. There was no correlation between major rating scales and light responses in the patient group. HAM-D r=0.135; HAM-A r=0.388; BR Mania r=-0.136; SOMA r=-0.175. The mean light response for the controls was 10.43 (SD=5.08, SEM=1.53). The mean light response for the patients was 7.35 (SD=4.87, SEM=1.62), t=1.379; df=18; $p<0.10$. There was a trend for the light responses (LR) to be lower in the patients vs. controls; however, the difference was not statistically significant at the p0.5 level.

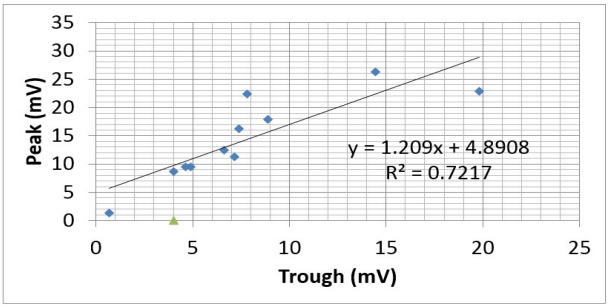

Fig. 1 . Peaks (light phase) vs. troughs (dark phase) in controls

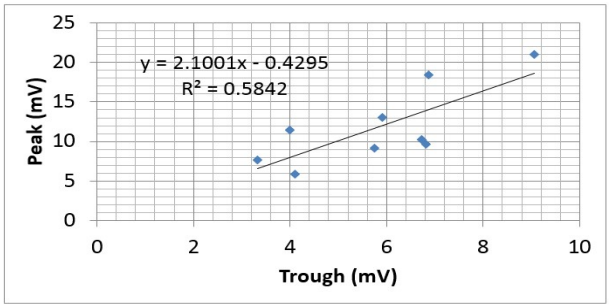

Fig. 2 . Peaks (light phase) vs. troughs (dark phase) in patients

A comparison of peaks and troughs in patients and controls revealed no significant difference. For the peaks, means (SD) for controls=14.39 (7.46); means of patients=11.85 (4.95); t=0.911; df=18; NS. For the troughs, means (SD) for controls=7.85 (5.24); means (SD) of patients=5.84 (1.80); t=1.11; df=18; NS. For the controls, the peak and trough correlation coefficient was r=0.854; t=4.34; df=7; $p<0.005$. For the patients, the peak and trough correlation coefficient was r=0.770; t=3.62; df=9; $p<0.005$.

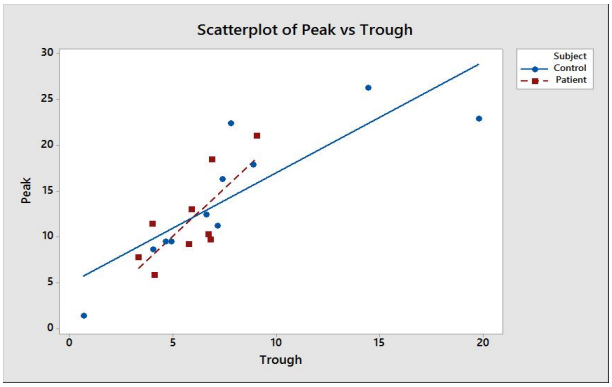

Fig. 3 . Peaks and troughs of controls and patients

In Figure 3, an Analysis of Covariance (ANCOVA) revealed no significant group difference (t=1.13; $p>0.2$) but this may have been due to the restricted range of peaks and troughs. With regard to the Arden ratio or peak/trough values, the mean P/T ratio in controls = 1.967. For the patients, the mean P/T Ratio = 2.04. Wilcoxen Z = 0.380 ($p>0.3$ not significant).

DISCUSSION

This study showed a trend but not a statistically significant reduction in light responses, i.e. reduction in dopamine production and release in the retinas of cocaine users during withdrawal vs. controls. Although there is some evidence to support the hypothesis of dopamine deficiency due to chronic cocaine use, the results in this study and others reveal that the brain is more resilient than previously thought. Cocaine use is not associated with destructive neuronal processes as in Parkinson's disease. Compensatory mechanisms may develop over time to overcome depleted dopamine levels in the brains and retinas of humans exposed to chronic cocaine. Radioactive ligand binding studies have revealed increased, decreased and unchanged brain densities of striatal dopamine transporters in laboratory animals exposed to cocaine. Studies have revealed conflicting results regarding densities of dopamine receptor binding sites in humans who have died of cocaine overdoses [12]. Reduced numbers of dopamine transporters in the nucleus accumbens have been found in some cocaine addicts which would enhance dopamine effects at postsynaptic receptor sites by blocking reuptake [10]. Other studies in animals showed reductions in electrical firing activity of dopaminergic cells in the substantia nigra and ventral tegmental area [20], transient changes in dopaminergic mRNA levels [21] and increased activity of Tyrosine Hydroxylase (TH), the rate limiting step in dopamine synthesis [22]. One study showed no significant changes in the mRNA levels of dopamine transporters, D1 or D2 receptors or the enzyme tyrosine hydroxylase in 21-day old rats exposed to cocaine in utero [23]. The density of large TH

cells was higher, and that of small TH amacrine cells was lower, in the temporal hemiretinas of rats exposed to prenatal cocaine vs. controls resulting in the negation of any overall effects of cocaine in these areas of the retinas [24]. Some studies demonstrated an increase in dopamine release due to long term changes in calcium transduction [10].

3,4-Dihydroxyphenylacetic Acid (DOPAC) is an intermediate produced in dopamine metabolism from the enzyme MAO-B. DOPAC/ DA ratios in the striatum are 1000:1 whereas the ratio in the retina is 1:1 meaning that dopamine is metabolized at a much higher rate in the striatum than in the retina. Therefore, higher concentrations of dopamine are present in the extracellular milieu of the retina compared to the striatum [17]. Light and circadian rhythms cause retinal dopamine levels to increase at dawn when vision switches from rod mediated to cone-mediated [17].

Patients with higher cocaine craving scores displayed a reduced (<0.5 microvolts) blue cone b wave ERG response suggesting that patients with low retinal dopamine levels and likely low dopamine levels in the mesolimbic and mesocortical pathways displayed higher craving [25].

Further studies are needed to determine if genetic polymorphisms, epigenetic changes from environmental insults or traumas and metabolic or hormonal disturbances which can predispose persons to drug use or other forms of addictions [4] are linked to baseline dopamine deficiencies. More clarification would be helpful to correlate frequency and duration of cocaine use and length of withdrawal from cocaine with dopamine function in vivo. Limitations of this study include the small number of patients and controls, neglect of more comprehensive history taking including frequency and duration of cocaine use as well as the administration of cocaine craving scales, and the lack of consideration of diurnal variations in the production of dopamine due to circadian rhythms as experiments were conducted throughout the day at different times for each subject.

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— This article does not have any appendix. —