Published in final edited form as:

Psychopharmacology (Berl). 2006 October ; 188(2): 228–235.

Emotion-based decision-making in healthy subjects: short-term effects of reducing dopamine levels

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Abstract

Introduction—Converging evidences from animal and human studies suggest that addiction is associated with dopaminergic dysfunction in brain reward circuits. So far, it is unclear what aspects of addictive behaviors are related to a dopaminergic dysfunction.

Discussion—We hypothesize that a decrease in dopaminergic activity impairs emotion-based decision-making. To demonstrate this hypothesis, we investigated the effects of a decrease in dopaminergic activity on the performance of an emotion-based decision-making task, the Iowa gambling task (IGT), in 11 healthy human subjects.

Materials and methods—We used a double-blind, placebo-controlled, within-subject design to examine the effect of a mixture containing the branched-chain amino acids (BCAA) valine, isoleucine and leucine on prolactin, IGT performance, perceptual competency and visual aspects of visuospatial working memory, visual attention and working memory, and verbal memory. The expectancy-

valence model was used to determine the relative contributions of distinct IGT components (attention to past outcomes, relative weight of wins and losses, and choice strategies) in the decision-making process.

Observations and results—Compared to placebo, the BCAA mixture increased prolactin levels and impaired IGT performance. BCAA administration interfered with a particular component process of decision-making related to attention to more recent events as compared to more distant events. There were no differences between placebo and BCAA conditions for other aspects of cognition. Our results suggest a direct link between a reduced dopaminergic activity and poor emotion-based decision-making characterized by shortsightedness, and thus difficulties resisting short-term reward, despite long-term negative consequences. These findings have implications for behavioral and pharmacological interventions targeting impaired emotion-based decision-making in addictive disorders.

Keywords

Amino acid; Prolactin; Human; Emotion; Dopaminergic; Dopamine; Cognition; Behavior

Introduction

Substance-use disorders are a major public health concern. In the United States, their 12-month prevalence rate is 9% (Kessler et al. 2005). Most of the drugs of abuse increase dopaminergic activity, and converging evidences from animal and human studies hypothesize that addiction is associated with dopaminergic dysfunction (as reviewed by Kalivas and Volkow 2005). It has been suggested that individuals with addictive behaviors have reduced dopamine (D2) receptor density and dopamine release resulting in a decreased sensitivity of reward circuits to stimulation by natural rewards (Volkow et al. 2004). Human neurobiological evidence for this hypothesis has been provided by functional imaging studies integrating measures of cerebral glucose metabolism and striatal dopamine (D2) receptor availability in adult subjects dependent on drugs of abuse (e.g., cocaine, methamphetamine, opiates, and alcohol).

It is unclear, however, how addictive behaviors are related to a decreased dopaminergic activity (Kalivas and Volkow 2005). One possibility is that a deficit in dopaminergic activity is associated with impaired emotion-based decision-making. According to the somatic marker hypothesis (SMH), decision-making is based on emotions or affective information related to visceral, somatic states connected with rewards and punishments (Bechara et al. 1997). A deficiency in dopaminergic activity may result in heightened affective reactions leading to impaired decision-making. The Iowa gambling task (IGT) is a laboratory task specifically developed to provide empirical support for the SMH, which was proposed to address the problems of decision-making encountered in patients with certain kinds of prefrontal damage and with compromised emotions (Bechara et al. 1994). Somatic markers (SMs) are conceived as a special instance of feelings generated from secondary emotions. Those emotions and feelings have been connected by learning to predict future outcomes of certain scenarios. When a negative SM is juxtaposed to a particular future outcome, the combination functions as an alarm bell. When a positive SM is juxtaposed instead, it becomes a beacon of incentive. On many occasions, SMs may operate covertly (without coming to consciousness). Thus, the centrality of emotion to the SMH is evident, as is the notion that SMs are emotion-related signals, which are either conscious or unconscious (Bechara et al. 1997). Because of the close links between the IGT and the SMH, and the previous experimental work showing close connections between performance of the IGT and the generation of emotion-related signals (in the form of anticipatory skin conductance responses), the IGT is a decision-making task involving an emotion-based component.

Several studies found a specific impairment of the IGT in subjects abusing alcohol (Mazas et al. 2000; Bechara et al. 2001), psychostimulants (Bechara et al. 2001; Bolla et al. 2003), opiates (Petry et al. 1998; Mintzer and Stitzer 2002), marijuana (Whitlow et al. 2004; Bolla et al. 2005), and in polysubstance abusers (Grant et al. 2000). Furthermore, there is evidence that decision-making is sensitive to changes in dopaminergic activity. The administration of *d*-amphetamine increases the value of delayed rewards relative to immediate rewards in rodents (Richards et al. 1999; Wade et al. 2000) and in healthy humans (de Wit et al. 2002). Several studies have looked at the effects of monoamines on reversal learning, i.e., the ability to shift response from a stimulus that is no longer rewarded to a stimulus not previously associated with a reward. In rats, lesions of the dopaminergic system in the ventral striatum disrupt reversal learning (Taghzouti et al. 1985). L-Dopa withdrawal studies in patients with Parkinson's disease suggest that a decrease in dopaminergic activity impairs reversal learning measured by task switching on the Cambridge gambling task (Cools et al. 2001, 2003). Czernecki et al. (2002) reported that patients with Parkinson's disease have deficits on both a reversal task and the IGT, neither of which was sensitive to L-dopa. Recently, Scarnà et al. (2005) assessed the effect of a decrease in dopaminergic activity on prolactin and attention toward different emotional cues outside of a learning context (probability of winning, reward, or punishment signals) when making risky choices in 32 healthy subjects. They compared the effects of placebo and a mixture containing 2 g of tryptophan and 60 g of branched-chain amino acids (BCAA) valine, isoleucine, and leucine. Dopamine synthesis is dependent on the availability of its precursor amino acids tyrosine and phenylalanine. Acute administration of a BCAA mixture has been demonstrated to lower the plasma ratio of tyrosine + phenylalanine to BCAA and to increase prolactin levels secondary to a decrease in dopaminergic activity (Harmer et al. 2001; Gijssman et al. 2002). By binding to dopamine D2 receptors, dopamine suppresses the high intrinsic activity of the pituitary lactotrophs secreting prolactin, through the regulation of calcium fluxes into the cells (Ben-Jonathan and Hnasko 2001). Compared to placebo, the tryptophan/BCAA mixture increases prolactin levels and reduces the sensitivity to the magnitude of losses in a decision-making task involving choices between outcomes with different magnitudes and probabilities. Increases in prolactin levels suggest that the effect of the BCAA mixture was related to dopamine depletion.

Thus, these studies suggest that dopaminergic activity modulates the delay, magnitude, and valence or emotional values of outcomes in decision-making.

To investigate the effect of a decreased dopaminergic activity on specific components of emotion-based decision-making in healthy human subjects, we used a double-blind, placebo-controlled, within-subject design comparing the effects of a single oral dose of a BCAA mixture and a placebo on prolactin levels and performance of the IGT. We used a cognitive computational model, the expectancy-valence model (Busemeyer and Stout 2002; Yechiam et al. 2005) to identify the relative contributions of distinct components (attention to past outcomes, relative weight of wins and losses, and choice strategies) to decisions made during performance of the IGT. We hypothesized that BCAA administration would be associated with decrements in IGT performance, as well as an increase in serum prolactin levels. Previous studies suggest that dopamine depletion is associated with deficits in visual spatial processing (Lichter et al. 1988), working memory (Goldman-Rakic and Selemon 1997), maintenance of cognitive set and cognitive flexibility, set shifting, and attention (Nieoullon 2002). To control for the effects of the BCAA mixture on cognition, we assessed perceptual competency and visual aspects of visuospatial working memory with the delayed match to sample (DMS) task (Lencz et al. 2003), visual attention and working memory with the continuous performance task-identical pairs (CPT-IP) (Cornblatt et al. 1988), verbal memory with the Hopkins verbal learning task (HVLT) (Brandt and Benedict 1991), and general cognitive abilities with the wide-range achievement test (WRAT)-3 reading subtest (Wilkinson 1993).

Materials and methods

Subjects

Subjects were recruited through advertising in local newspapers. Present and past histories of psychiatric disorders were ruled out by the use of the structured clinical interview for DSM-IV axis I disorders (SCID)—non-patient edition (First et al. 2001). A first-degree relative history of psychotic or affective disorders was ruled out by the use of a family history questionnaire (available upon request). Subjects with a history of serious medical illness, drug or alcohol use disorders, or use of any psychoactive medication during the past year were ruled out. The study was conducted according to the guidelines of the Institutional Review Board of the North Shore—Long Island Jewish Health System (Lake Success, NY, USA). Eleven healthy Caucasian men volunteers participated in this study after providing written informed consent. The mean age was 27 ± 7 (SD) years old (range=18–41). The mean level of education was 14 ± 2 (SD) years (range=10–18). All subjects had normal results on physical examination and negative urine toxicology, and were paid for their participation in the study.

Experimental design and general procedures

We used a double-blind, placebo-controlled, within-subject design to look at the effect of a single oral dose of a BCAA mixture on IGT performance. The study consisted of two challenge tests during which either a BCAA mixture or a placebo was given. To control for a possible practice effect in the performance of the IGT, we used a counterbalanced design, i.e., half of the subjects had the placebo condition first, and another half of the subjects had the BCAA condition first. BCAA mixtures are palatable and well tolerated in healthy control and patient populations (Harper et al. 1984; Berry et al. 1990; Richardson et al. 1999). BCAA-containing compounds are available as nutritional food supplements at vitamin and health food stores. One formulation, Tarvil® (SHS North America, Gaithersburg, MD, USA), is a pineapple-flavored drink and contains BCAA in the following composition: valine:isoleucine: leucine 3:3:4 by weight, in addition to flavoring additives. We used the following dosage: 18 g valine, 18 g isoleucine, and 24 g leucine. This dosage was chosen because it has been shown to induce a significant prolactin response in healthy subjects (Gijsman et al. 2002). The placebo was made by Ettinger Pharmacy (Garden City, NY, USA). It consisted of a pineapple-flavored mixture with the same consistency as Tarvil®. The order of Tarvil® and placebo was randomized. Test days were separated by at least 2 days but by not more than 1 week. Subjects fasted (except for water intake) and did not smoke after midnight before each study day. All administrations of Tarvil® and placebo took place at the same time of the day (around 10 a.m.). The period of time between tests and the fasting period before tests were chosen to minimize any potential carryover effects as BCAA have a half-life of about 1.5 h and take approximately 8 h to clear (Marchesini et al. 1987).

Biological measures

In the morning of each study day, a heparinized intravenous access was placed for the repeated blood measurements of prolactin levels. Plasma samples for prolactin measurement were collected every hour up to 5 h from the time of administration of Tarvil® or placebo. Intravenous access was removed after the last blood draw. Vital signs were assessed hourly.

Behavioral measures

Two hours after the administration of Tarvil® or placebo, the following tests were administered in the same order in both study conditions:

Iowa gambling task (IGT)—In this computerized task (Bechara 2005), subjects make choices from four different decks of cards. Two decks (A' and B') yield high immediate reward

(monetary reward) but lead to long-term losses (i.e., these are the disadvantageous decks). The other two decks (C' and D') yield relatively low immediate reward, but they lead to long-term gain (i.e., these are advantageous decks). The location of the decks was the same in all IGT procedures. At the beginning of the task, subjects receive a hypothetical loan of play money (*\$2,000). Each deck has 60 cards. Subjects are allowed to make 100 choices, and the goal of the task is to maximize profit.

The following variables were used for data analysis: (1) total amount of money won or lost after 100 trials; (2) net scores of selected cards $[(C'+D')-(A'+B')]$ chosen in 20 card selection intervals (i.e., five repeated measures given a total of 100 card selections), which assess the subject's ability to maximize profit by switching from disadvantageous to advantageous decks over time; (3) total net score (i.e., the sum of the five net scores); and (4) parameters of the expectancy-valence model (Busemeyer and Stout 2002; Yechiam et al. 2005). The *recency parameter* is a measure of attention to past outcomes. It has a value between 0 and 1. High values mean that the subject is attentive to more recent outcomes compared to more distant outcomes. In contrast, low values mean that the subject is attentive to distant outcomes. The *attention to losses/wins parameter* measures the relative weight of losses and wins and has a value from 0 (attention to losses only) to 1 (attention to gains only). The *choice consistency parameter* measures how the decision maker is consistent in his/her choice and is related to response mechanisms (e.g., boredom, recklessness, and impulsiveness). It has a value between -5 (choices are random and independent of expectancies) and +5 (choices are highly dependent on expectancies, i.e., the deck with the largest expectancy is chosen with certainty).

Cognitive tests

- 1) The DMS task (Lencz et al. 2003) assesses both perceptual competency (similar to span of apprehension) and visual aspects of visual-spatial working memory. Delays of 4 and 8 s between the criterion pattern and test patterns provide a parametrically altered assessment of load on visual-spatial working memory.
- 2) The CPT-IP (Cornblatt et al. 1988) is a computer-generated measure of visual attention and working memory designed to detect subtle information processing dysfunction. The primary response indices generated by this task are: correct responses (or hits) (%), false alarms (%), and random errors (%). Reaction times for all responses and the signal detection indices, d' and log beta, are calculated.
- 3) The HVLT (Brandt and Benedict 1991) consists of 12 words that are orally presented over three immediate-recall trials, followed by a delayed-recall trial (20–25 min interval), and a yes/no recognition trial. The HVLT provides indices of free recall (the total number of immediately recalled words across the three trials), delayed recall (the number of words recalled after a delay of 20–30 min), and recognition discrimination.
- 4) The WRAT-3 reading subtest (Wilkinson 1993) assesses single-word reading skill and is a measure of general cognitive abilities in healthy individuals. In this task, the subject is required to read 75 words of increasing difficulty. Scoring is based on correct pronunciations of the words; raw scores, age corrected percentile and standard scores, and grade equivalent ratings may be computed.

Symptom and side-effect ratings

Mood, anxiety, and psychotic (positive and negative) symptoms were assessed 1 h before (9 a.m.), 4 h (2 p.m.), and 6 h (4 p.m.) after the administration of the study mixture with the Hamilton rating scale for depression—24 items (Hamilton 1960), brief psychiatric rating scale (Overall and Gorham 1988; Woerner et al. 1988), and scale for the assessment of negative symptoms (Andreasen 1989).

Side effects were assessed at the same time as symptoms with the Simpson–Angus scale (Simpson and Angus 1970). Subjects were also asked if they had other side effects to report.

Data analysis

A mixed model approach to repeated measures analysis of variance (RM ANOVA) was performed separately on prolactin (with two repeated factors: time and drug condition), total amount won or lost at the IGT (with one repeated factor: study drug condition), net scores (with two repeated factors: blocks of trials and study drug condition), total net score, recency parameter, attention to losses/wins parameter, choice consistency parameter, and DMS, CPT-IP, HVLIT, WRAT-3 scores (with one repeated factor: drug condition). In all RM ANOVAs, the order of the treatments is a between-subject factor. The study drug by order interaction was removed from the model if it was not significant. All statistics were performed using SAS version 9.1 for Windows (SAS Institute, Cary, NC, USA).

Results

Six subjects had the placebo condition followed by the BCAA condition. Five subjects had the BCAA condition followed by the placebo condition. The time interval between study drug conditions was 3 to 6 days. Tarvil[®] was well tolerated, and subjects reported no changes in symptoms or side effects. Table 1 summarizes the results for plasma prolactin levels and the IGT.

Prolactin levels

There was a significant time by study drug interaction ($F=7.97$, $df=5.50$, $p<0.001$) but no significant effect for order of the tests ($F=0.07$, $df=1.9$, $p=0.79$). Prolactin levels, as the function of time elapsed after BCAA/placebo administrations, are graphed in Fig. 1.

Iowa gambling task

Total amount lost/won—There was a significant main effect for study drug ($F=6.41$, $df=1.9$, $p=0.03$) but no significant effect for order of the tests ($F=0.09$, $df=1.9$, $p=0.77$). The interaction of study drug by order of the tests was not significant.

Net scores—There was no significant effect of time ($F=0.36$, $df=4.40$, $p=0.83$), study drug ($F=1.61$, $df=1.10$, $p=0.23$), or order of the tests ($F=1.37$, $df=1.9$, $p=0.27$). Least square means (LSM) of net scores are graphed in Fig. 2. Although there were no statistical differences between study drugs for net scores, the graph suggests a worsening of net scores over time in the BCAA group.

Total net score—There was a trend for a main effect of study drug ($F=3.78$, $df=1.9$, $p=0.08$) and no significant effect for order of the tests ($F=1.38$, $df=1.9$, $p=0.27$). There was no significant correlation between peak change in prolactin levels and total net score.

Expectancy-valence model

Recency parameter—There was a significant main effect for study drug ($F=5.98$, $df=1.9$, $p=0.04$). The recency parameter was higher in the placebo condition [LSM=0.59±0.14 (standard error of LSM)] compared to the placebo condition [LSM=0.29±0.07 (standard error of LSM)]. There was no significant effect for order of tests ($F=2.86$, $df=1.9$, $p=0.12$). The interaction of study drug by order of the tests was not significant. There was no significant correlation between peak change in prolactin levels and recency parameter.

Attention to losses/wins parameter—There was no significant effect for study drug ($F=0.54$, $df=1.9$, $p=0.48$) nor for order of the tests ($F=0.01$, $df=1.9$, $p=0.92$).

Choice consistency parameter—There was no significant effect for study drug ($F=3.34$, $df=1.9$, $p=0.10$) nor for order of the tests ($F=0.70$, $df=1.9$, $p=0.43$).

Neurocognitive tests (DMS, CPT-IP, HVLIT)—There was no significant effect for study drug nor for order of the tests for any of the primary outcome variables.

Discussions

Our results indicate that BCAA impair aspects of emotion-based decision-making, as well as decrease central dopaminergic activity. The worsening of IGT net scores over time in the BCAA condition is in agreement with the hypothesis that biological mechanisms by which somatic markers exert their influence on decision-making are mediated through neurotransmitter systems such as dopamine (Bechara 2005). Specifically, BCAA administration interferes with a particular component process of decision-making related to attention to more recent events as compared to more distant events, thus altering the quality of one's decisions. These data are consistent with previous studies indicating that increased dopaminergic activity associated with *d*-amphetamine administration increased the valence of delayed rewards relative to immediate rewards in rodents (Cardinal et al. 2000; Wade et al. 2000) and in healthy humans (de Wit et al. 2002). In our study, we find that a BCAA-induced decrease in dopaminergic activity reduces the influence of past outcomes on making decisions. This suggests that dopamine plays a key role in modulating the influence of time of past and future outcomes on decisions. One possible explanation for our findings involves the critical role of the prefrontal dopamine system in attentional control and working memory (for a review, see Robbins 2005). A decrease in dopaminergic activity may destabilize representations, resulting in attention for more recent events. Our results seem also to corroborate the hypothesis of a differential susceptibility of dorsolateral and orbitofrontal cortex-dependent tasks to dopaminergic tone (Robbins 2005). A BCAA-induced, decreased dopaminergic activity may affect the orbitofrontal circuitry, but not the dorsolateral circuitry, and may explain our negative cognitive findings. Thus, dopamine may modulate the ability to process past information, and reduced dopaminergic activity after the administration of BCAA results in a tendency to focus on the most recent information.

If replicated, these findings will have important implications for the understanding and treatment of subjects with substance-use disorders. A decrease in dopaminergic activity has been hypothesized in several substance-use disorders (Kalivas and Volkow 2005), and addictive behaviors may improve with pharmacological interventions that increase dopaminergic activity. The dopaminergic effects of some anticraving medications seem to corroborate this approach. Bupropion, a smoking cessation aid, is a dopamine reuptake inhibitor (Stahl et al. 2004). It has also been suggested that disulfiram reduces the frequency of cocaine use by inhibiting dopamine beta hydroxylase, thus increasing dopamine levels (O'Brien 2005). By increasing dopaminergic activity, pharmacological treatments may help patients with substance-use disorders to avoid harmful long-term outcomes by making better decisions.

Our study has some limitations. There may be a practice effect with repeated administration of the IGT. However, to control for the practice effect, half of the subjects had the placebo condition first, and another half of the subjects the BCAA condition first. We also controlled for the counter-balanced design in the statistical analysis. The difference in amount lost/won on the gambling task between study drug conditions was significant at $p<0.032$, and we did not apply a Bonferroni-like adjustment, where a significant p value would be considered to be

<0.01. Our negative findings for correlations between peak prolactin changes and total net scores or values of the recency parameter may be due to the small sample size. Future studies with larger sample sizes should yield more information regarding these relationships. Although not significant, mean score for the choice consistency parameter in the placebo condition was lower than expected and was most probably fortuitous due to the small sample size. Choice consistency in the BCAA condition was similar to choice consistency reported in previous studies with healthy subjects (e.g., Busemeyer and Stout 2002). A BCAA mixture lowers the ratio of tryptophan to BCAA (Gijsman et al. 2002), which may impair decision-making through an effect on serotonergic function. However, this is unlikely because serotonin increases prolactin release, and a decrease in serotonergic function would have resulted in decreased prolactin release (Gijsman et al. 2002). Furthermore, Scarnà et al. (2005) added tryptophan to BCAA and found a similar increase in plasma prolactin levels, suggesting that the effect of a BCAA mixture on prolactin is not related to a decreased serotonergic function. Finally, tyrosine depletion induced by BCAA administration may decrease noradrenergic activity, which has been found to impair decision-making by attenuating the processing of punishment cues (Rogers et al. 2004). However, tyrosine depletion does not seem to alter noradrenergic function in humans (Harmer et al. 2001).

In conclusion, we found that the acute administration of a BCAA mixture in healthy men subjects is associated with increased prolactin levels and changes in a particular component process of decision-making related to attention to more recent events as compared to more distant events, thus altering the quality of one's decisions. These findings may have important implications for the development of treatment strategies targeting the dopaminergic system in addictive disorders. The high sensitivity of dopaminergic activity to the balance of BCAA in the diet has also implications for understanding the consequences of certain dietary regimes on decision-making. BCAA regimens are widely available to the public and are promoted to body-builders and obese individuals as dietary supplements to "increase the lean muscle mass". One may wonder if BCAA diets promote or worsen the abuse of anabolic steroids among bodybuilders and weightlifters. Lastly, many dieting individuals are described as restrained eaters, as they exert tremendous effort and energy to curb their food intake to lose weight. BCAA dietary supplements may be responsible for a loss of self-control after a successful period of restraint.

Acknowledgements

This work was supported by grants NIDA K23 DA015541 (SS) and NIMH K23 MH001760 (AKM), and grants from the National Alliance for Research on Schizophrenia and Depression (NARSAD) and the Stanley Medical Research Institute (AKM). We thank Drs. Terry Goldberg and Nina Schooler for their helpful comments.

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Fig 1.
Prolactin levels after the administration (10:00 a.m.) of placebo or branched-chain amino acids (BCAA)

Fig 2.
IGT net scores after the administration (10:00 a.m.) of placebo or branched-chain amino acids (BCAA)

Table 1

Least square means (LSM) and standard error of the least square means (SELSM) for prolactin and the gambling task in the placebo and BCAA conditions

	Placebo (LSM±SELSM)	BCAA (LSM±SELSM)	<i>p</i>
Prolactin levels			<0.0001 ^a
10 a.m. (baseline)	9.88±0.94	9.77±1.95	
11 a.m.	9.95±0.94	8.88±1.95	
12 p.m.	8.29±0.94	12.09±1.95	
1 p.m.	9.45±0.94	21.00±1.95	
2 p.m.	10.25±0.94	18.43±1.95	
3 p.m.	11.01±0.94	13.12±1.95	
Gambling task			
Total amount lost/won (*\$)	-630±288	-1404±305	<0.04
Net scores			
Trials 1–20	0.67±2.25	2.41±2.73	N.S.
Trials 21–40	1.24±2.20	0.50±1.14	N.S.
Trials 41–60	3.51±1.91	1.15±2.02	N.S.
Trials 61–80	2.93±3.10	-2.16±2.38	N.S.
Trials 81–100	4.22±2.42	-1.51±2.64	N.S.
Total net score	12.64±5.54	0.27±5.10	0.08
Value valence-expectancy model			
Recency parameter	0.29±0.07	0.59±0.14	<0.04
Attention to losses/wins parameter	0.55±0.14	0.64±0.15	N.S.
Choice consistency parameter	-2.32±0.86	0.12±1.06	N.S.

^aTime by study drug interaction