Enhancement of Attention Processing by Kantroll™ in Healthy Humans: A Pilot Study

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P300

INTRODUCTION

One of the most intriguing discoveries in neurobiology was that certain neurotransmitters, e.g., dopamine, norepinephrine, epinephrine, serotonin, melatonin and glycine, which play vital roles in mood regulation, can be dramatically influenced by the circulating levels of their precursor amino acid nutrients.[1,2] Not surprisingly, then, measurements of brain chemical turnover in animals have demonstrated changes in neurotransmitter levels following precursor amino acid loading.[3] Complementary behavioral changes also have been demonstrated in animals following systemic and direct central nervous system delivery of precursor amino acids.[4] While certain L-amino acids are neurotransmitter and neuromodulator precursors, their racemates the D-amino acids also have biological activity. For example, D-phenylalanine and D-leucine decrease the degradation of opioid peptides, which are also central to regulation of mood.[5]

Neurotransmitter actions form the neurochemical basis of behavior, and their perturbation may underlay a variety of psychiatric and behavioral disorders.[6-8] Specifically, anomalous regulation of dopamine, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), glutamine, and the opioid peptides are thought to play crucial roles in the addictive disorders, particularly those involving alcohol and cocaine abuse.[9] Consequently, these observations have provided momentum to the idea that ingestion of selected nutrients could affect mood and therefore behavior in humans. While nutritional strategies have been employed in the past,[10] demonstrations of effectiveness have been decidedly limited. Recent clinical data, however, suggest a substantive effect of a combination of amino acid precursors and enkephalinase inhibitors on recovery from alcohol and cocaine addictions.[11] In particular, one pertinent study suggested the usefulness of an amino acid supplement, Tropamine™ (forerunner of Kantroll™), in a population of cocaine abusers.[12]

The focus in this report concerned the effects of Kantrol™ on attentional processing because, in part, alternations in attention/or concentration both precede and accompany sustained substance abuse,[13,14] and because many of the transmitter substrates thought to be important in attention are targeted for manipulation through the administration of Kantroll.™ Specifically, the focus was upon select components of the cognitive event-related potential (ERP) evoked by two visual attention tasks. Both attention probes generated a family of components comprising the ERPs, each representing a specific stage of information processing. In general, however, the various components can be divided up into two groups: those of a more automatic nature (independent of the meaningfulness of the stimuli) and

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Table 1

Composition of Kantrol™ in mg per capsule.*

Ingredient	MG/Capsule
DL-Phenylalanine	250
L-Tyrosine	150
L-Glutamine	50
Zinc	5
Magnesium	25
Calcium	25
Vitamin B-1	1.67
Vitamin B-2	2.5
Vitamin B-12	0.005
Niacin	16.7
Pantothenic acid	15
Pyridoxal-5-phosphate	20
Vitamin C	600
Chromium	0.06
Iron	9
Folic acid	0.067

*An improved formulation is available.

those of a more controlled nature, contingent upon the meaningfulness of the stimuli. The N2 component was selected as the representative of automatic processing and the P300 component as the representative of controlled operations, dependent upon the context in which the stimulus is embedded. Of interest, prefrontal and temporal zones have been posited to be important for the mediation of more controlled aspects of attention.[15-17] Employing specifically designed behavioral probes has an advantage over a more conventional EEG analysis in that the specific systems important to attentional processing are challenged. Another advantage relates to the 'state-dependency' of the P300 component,[18] which makes it a potentially sensitive measurement operation for monitoring the improvement of cognitive functioning associated with various interventions. This study, then, addressed the issue of the electrophysiological and performance correlates of chronic Kantrol™ administration on normal subjects, especially as indexed by changes in the representatives of automatic and controlled components of the cognitive ERP.

METHODS

Subjects

This study involved 20 nonreferred, right-handed, male subjects (average age = 25.6 years) recruited from a freshman medical school class. The students were interviewed by a Clinical Neuropsychologist (JDF) and judged to have histories negative for psychological, neurological, or psychiatric conditions. All subjects were free of prescription medications, and each signed an informed consent and an agreement to take the capsules according to protocol. The subjects were compensated for participation in the study. The subjects performed the entire test battery twice, forming a test-retest model, so that the individual subject acted as his own control. Initial testing was done on day zero (pre-test) and then again after 28-30 days (post-test). In between, the subjects consumed six Kantrol™ capsules daily for 28-30 days. The composition of Kantrol™ is shown in Table 1. The data from two subjects were not included because of poor quality of either the pre-test or the post-test recordings.

Performance Tasks

Two performance paradigms were used to elicit electrophysiological responses: a) Spatial Orientation - This is a reaction time task (SOT), championed by Posner et al[19,20] where 'priming cues' were presented in the left and right visual fields, and reaction times were compared for when the 'priming cues' were and were not available. Through a comparison of reaction times, it allowed for an assessment of the individual's ability to switch attention smoothly between the visual fields. As structured, this task evaluated a more elemental stage of attentional processing that pertains to the more covert operations of attention, and tends to load more heavily on the more automatic stages of attention.[20,21]

The instructions were to focus on a cross in the center of the monitor screen and push the right mouse button when the '*' appeared in the right box, and the left button when the '*' appeared in the left box. The boxes alternated with respect to which one was the brighter. Response times were recorded, and ERPs were constructed, with respect to four categories: (1) facilitated for the right visual field, (2) nonfacilitated for the right visual field, (3) facilitated for the left visual field, and (4) nonfacilitated for the left visual field. The presentation was randomized, but with an equal probability for the four conditions. The facilitated box was brightened 500 msec prior to the presentation of the target to serve as the 'priming cue.'

b) Contingent Continuous Performance - The Contingent Continuous Performance Task (CCPT) was a variant of a classic theme,[22] incorporating elements of both selective and sustained attention. This task was analyzed primarily in regards to quality of performance to index the more controlled stages of attentional pro-

cessing. Letters of the alphabet were presented one at a time in the center of the screen. Basically, the individual was asked to respond with his dominant hand, by pressing the left mouse button, to a specific letter order: e.g., 'T' if immediately preceded by another 'T'. The initial 'T' in a pair of 'Ts' served as a Warning cue, with the second 'T' being the Target. All other letters were considered Distractors, which were to be ignored by the subject.

The probability of a non-'T' was set at 50%, the probability of the Warning 'T' was set at 30%, and the probability of the Target 'T' was set at 20%. Consequently, within each block 50% of the Warning 'Ts' were not followed by a Target 'T,' but rather by a Distractor letter. These were considered 'foils' or 'lures.' The 'foils' were added to invite a greater demand for selective attention. The electrophysiological responses to the 'foils' were not included in the analysis. This 'Fixed Rate' version had a constant interstimulus interval (ISI) of 0.8 sec, and a stimulus duration (on-screen time) of 0.2 sec. Together, there were 500 trials, and averaged ERPs were constructed according to one of three conditions: Distractor (any letter other than a 'T' or a 'foil'), Warning (the first 'T' in a pair), and Target (the second 'T' in a pair).

The principal performance measures were errors of omission and errors of commission, both of which were used for the calculation of block performance and the Grand Deviation Index (GDI).[23] The GDI provided an estimate of the degree and duration of inattentiveness, designed as a measure of consistency of performance. The performance was analyzed across the 10 blocks of stimuli, with an equal number of Targets, Warnings, and Distractors across all blocks. By subdividing the task into blocks, it allowed for viewing of performance over time in order to assess consistency of performance and possible vigilance decrements. It is noteworthy that the prefrontal cortex appears to be most heavily involved in sustaining attention and effort, which are important factors with regard to overall performance on this task, and are very sensitive to stimulant medication.[24]

Recording Scheme

The EEG was recorded from 28 active recording sites referenced to linked earlobes (A1-A2) as described elsewhere.[21,23] The onset of each stimulus presentation triggered an 800 msec sampling of EEG from which the ERPs were constructed; included in each epoch was a 100 msec prestimulus sampling that was used for baseline correction.

Data Analysis

Data was analyzed according to the following protocol. First, baseline correction procedures were applied using the average of the 100 msec prestimulus periods. Then the model EOG waveform was developed and subtracted from the waveforms associated with scalp locations, according to the regression algorithm described above, and a correction for slow blink artifacts. All trials containing VEOG/HEOG artifacts exceeding 100 ± μV were automatically rejected. In addition, individual trials were manually inspected for any remaining eye-movement, EMG, or movement-related artifacts, but all visual editing was conducted blind to the actual grouping of the subjects. When an electrode gave repeated spurious recordings for an individual, it was 'turned off' for the analysis, eliminating it from inclusion in the statistical analysis or construction of the maps. In cases where adjacent electrode sites were bad or where more than two electrodes gave artifactual records, that subject was eliminated from the sample.

There were three parameters examined, each of which may vary according to the efficiency of an individual's attentional processing. These parameters were: (1) latency, (2) amplitude, and (3) symmetry (spatial distribution) of components of the ERPs. The ERP components were identified with respect to the grand averaged ERP responses, where the latency was the time between the stimulus onset and the peak of the certain component, and peak amplitudes defined as the potential change between the 100 msec prestimulus baseline and the point of greatest amplitude. Trough-to-peak measurements were also performed in the preliminary analyses, but essentially no differences were noticed with respect to the components studied.

The statistical analysis proceeded in several stages. First, T-test statistical maps for the group averaged data were generated for all 28 electrode sites, at each point in time. This was a variation on the Statistical Probability Mapping of Duffy et al[25] resulting in easily visualized maps, pointing to electrode sites for which further analysis was indicated. For both the SOT and CCPT, the electrode sites selected for additional analysis were T5 and Pz to evaluate the N2 and P300 components, respectively. The statistical analyses were performed for components of the waveforms recorded in the Target condition, employing a paired T-test model where the Baseline and Treatment conditions were com-

pared. Performance data were also analyzed with the same model.

RESULTS

Before discussing the results, a brief preview of the relevant components elicited by these performance probes will be offered. After the primary visual response, the N2 component appeared, presenting with a bilateral posterior temporoparietooccipital distribution. This is a modality-specific component that seemingly reflects classification or categorization operations,[26] which is an early stage of the orienting response. This component develops in the hemisphere opposite to the visual field of stimulation.[21] Importantly, the N2 component is robust in appearance regardless of the salience of the eliciting stimulus. In contrast, the classic P300 component only emerged in the presence of a meaningful stimulus. This contextually-dependent component assumed a centroparietal distribution that was typically maximal in amplitude at Pz. This component is equivalent to the P3b component seen in other paradigms.[27-30] The changes in the N2 and P300 components associated with Kantroll™ treatment are the focus of the following discussion. Illustrative examples of the results from the two attention tasks are presented in Figures 1 and 2.

The results from the SOT will be discussed first. Again, this particular paradigm generates a number of components,[21] including the N2 negativity that developed within the 100-200 msec interval. The N2 component was found to be somewhat enhanced subsequent to treatment, but the amplitude change did not pass our established threshold for significance [$F(1,17) = 2.30$, $p = 0.0259$]. Nevertheless, late vertex positivity (i.e., P300 component) in the post-test condition was found markedly larger in amplitude for both the left [$F(1,17) = 8.531$, $p = 0.0095$] and right [$F(1,17) = 16.31$, $p = 0.009$] facilitated conditions. To better appreciate the treatment effects, topographical maps are shown in Figure 1 for the Baseline (Figure 1A) and Treatment (Figure 1B) conditions with respect to the facilitated (i.e., 'primed') condition for the left visual field. In the 100-200 msec intervals of Figure 1A and B, the N2 negativity is indicated over the right temporoparietal region. Again, the effects of Kantroll™ on this component approached statistical significance, but greater changes were associated with the P300 component and can be readily appreciated by comparing the P300 components from the 300-400 msec epochs in Figure 1A and B. Essentially, the topographical features of the P300 component remained the same, but the peak amplitudes were enhanced by the Kantroll™ treatment (Figure 1B). However, there were again no peak latency differences associated with treatment. The patterns for the facilitated condition with respect to the right visual field, as well as for the nonfacilitated conditions for both visual fields, were similar to those presented so they will not be described further.

With respect to the performance data, the combined reaction times from the facilitated conditions for the left and right visual field stimuli were faster after treatment (232 ± 0.03 msec versus 238 ± 0.03 msec [$F(1,17) = 8.62$, $p = 0.001$]). Hence, Kantroll™ treatment was found to promote better performance on this attention task, along with enhancing an important electrophysiological correlate of controlled attention. In addition, a marked effect was seen on the P300 component associated with a vigilance task (i.e., CCPT), where there was a greater demand for selective and sustained attention.

The various components of the cognitive ERPs associated with the Contingent Continuous Performance Task (CCPT) have many similarities to those generated by other continuous performance tasks, featuring a prominent P300 component. Three sets of waveforms were constructed for analysis - Distractor, Warning, and Target - but only the Target waveforms need to be discussed. In a manner similar to the analytic approach for the SOT, comparison of the Target waveforms between the pre-test and the post-test conditions found a significant [$F(1,16) = 7.422$, $p = .015$] enhancement of the P300 amplitude. On the other hand, there were again no appreciable differences in terms of peak latencies.

To illustrate the treatment effect, the grand averaged Target waveforms from Pz are shown in Figure 2A for the Baseline (red) and Treatment (black) conditions. The large positive-going potential, peaking around 300 msec, is the classic P300 component. Again, the Target waveforms were those taken when the subject responded to the second 'T' in a pair, as per the instructions. Figure 2B shows the topographical maps for the 300-400 msec interval for the Target conditions before (Baseline) and after (Treatment) Kantroll.™ Notice that the topographical features of the P300 component remained the same in both the Baseline and Treatment conditions, where the P300 component occupied a central posterior locus. As was the case for the

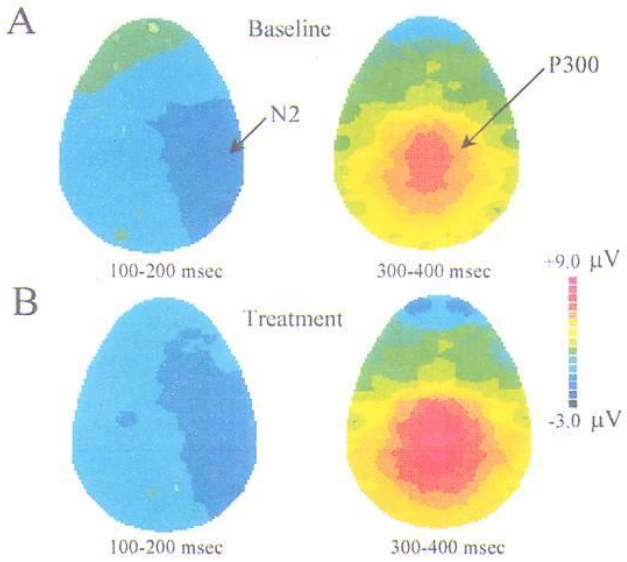

Figure 1.
Topographical maps from the Spatial Orientation Task (SOT) for the left facilitated condition. A. Maps generated from grouped data taken prior to treatment (i.e., Baseline) for the time domains of the N2 component (100-200 msec), and P300 component (300-400 msec). B. Maps generated from grouped data taken after Treatment (i.e., Kantroll™) for the time domains of the N2 component (100-200 msec), and P300 component (300-400 msec). The distributional patterns of the N2 and P300 components were similar in both instances, although the signal intensity was significantly enhanced following Kantroll™ administration.

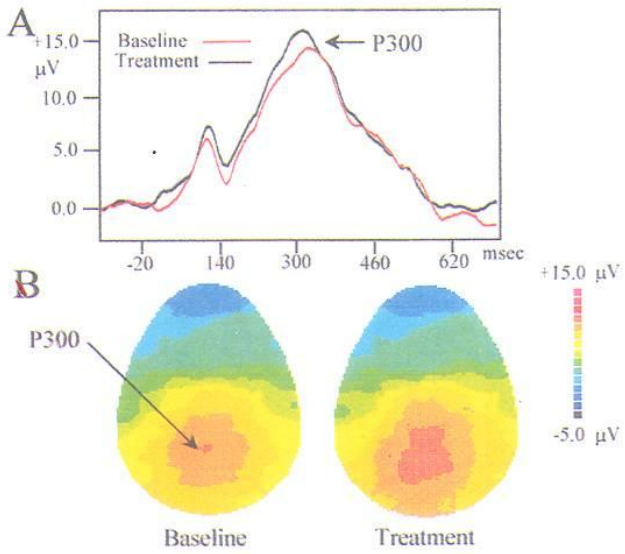

Figure 2.
A. Averaged ERPs resulting from the responses to target stimuli for the Contingent Continuous Performance Task (CCPT). The retest waveform (black line) was significantly greater for the P300 waveform than was the pre-test wave (red line). B. Topographic potential distribution maps for responses to a target stimulus at 300 msec post-stimulus. In the Treatment condition, the central zone (Pz) shows greater positivity than in the Baseline condition.

SOT, this component was essentially symmetric. Still, the amplitude of the P300 component was enhanced in the Treatment condition, as can be appreciated by comparing the components from the pre-test and post-test conditions. Again, there was a trend for an enhanced N2 component, but still the greatest changes were associated with the P300.

DISCUSSION

Kantroll™ (formerly Tropamine™) was designed as a potential treatment for cocaine abuse, with the recognition that one manifestation of cocaine abuse is altered attentional processing.[31] As one index of attentional competency,[32] the P300 was evaluated as a modality-independent byproduct of the selective attention process.[22] The deep portions of the temporal lobe have clear modulator responsibilities over the salience-dependent P300,[28,29] and it is precisely these regions that are implicated in the brain's response to cocaine. Hence, it is notable that this investigation found that treatment with Kantroll™ led to an enhancement of the P300 component of the cognitive ERP, and also to an improvement in cognitive processing speeds. This latter observation is consistent with the notion that Kantroll™ has a mild stimulant effect, which, in turn, may improve the efficacy of information processing. On the other hand, no significant difference emerged with respect to the main performance variable for the CCPT-GDI. The likely reason for this is that these normal subjects were already near their optimum performance with respect to accuracy. It might be expected, however, that performance differences would emerge in clinical populations. It should also be added that this investigation was part of a larger project where normal subjects were evaluated in a test-retest fashion with approximately a 1 month delay, with no intervening treatments, to establish reliability of these protocols. In the absence of any sort of pharmacological manipulation, the N2 and P300 components, as well as the other components, were found to be stable and did not show enhancements in the second recording session.

Pertinent to this study, attentional processing has been shown to be dependent on biogenic amine regulation.[33] Since the precursors for synthesizing the amines are dependent upon dietary intake, it is possible that dietary supplements can alter available biogenic amine stores in the brain. This has led to various clinical strategies that target nutritional improvement of the brain's chemistry for the treatment of specific disorders.[34] It is noteworthy that the ingredients for relevant neurotransmitters (including vitamins and minerals) have been found deficient not only in active alcohol and drug abusers but often remain in deficit well into recovery.[35] It is intuitive, then, that making use of normal cellular control mechanisms can result in decided improvement in psychological outlook, behavioral performance, and relapse prevention. These observations suggest that nutritional supplementation can, indeed, enhance neurophysiologic function in normal controls, and this seemingly has important implications for the use of amino acid supplementation in Reward Deficiency Syndrome (RDS), (cocaine, attention deficit disorder).[12,36]

These findings are also consistent with the implications of the Reward Cascade model[37] that neurotransmitters systems, altered as a consequence of drug use and/or genetic anomalies, can be manipulated to enhance brain functioning and thus potentially improve feelings, mood, and reward-deficient behavior.[38-40] Our results suggest that this could be accomplished, at least in part, by amino acid loading techniques.[41]

Most importantly, the interpretation of these results are necessarily guarded due to lack of placebo controls. A study in progress is investigating how various stages of attention processing are affected in both healthy volunteers and recovering cocaine abusers with proper placebo controls. But, also additional studies are needed to determine if critical neurotransmitter levels are, in fact, altered by precursor loading in populations of addicted individuals as well as attention deficit disorder (ADHD).

SUMMARY

This is the first report in humans of the effects of daily ingestion of a specific amino acid mixture, Kantroll,™ on cognitive event-related potentials (ERPs) associated with performance. Cognitive ERPs were generated by two computerized visual attention tasks, the Spatial Orientation Task (SOT) and Contingent Continuous Performance Task (CCPT) in normal young adult volunteers, where each subject acted as his own control for testing before and after 28-30 days of amino acid ingestion. A statistically significant amplitude enhancement of the P300 component of the ERPs was seen after Kantroll™ for both tasks, as well as improvement with respect to cognitive processing speeds. The enhancement of neurophysiologic function observed in this study on

normal controls is consistent with the facilitation of recovery of individuals with RDS (i.e., substance use disorder, ADHD, carbohydrate bingeing) following the ingestion of the amino acid supplement, Kantroll™, and warrants additional placebo-controlled, double-blind, studies to confirm and extend these results.

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