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Effects of cotinine on information processing in nonsmokers

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Abstract Cotinine, the major proximate metabolite of nicotine, is present in smokers in higher concentrations and for a longer time than nicotine, yet its effects on information processing have not previously been reported. We studied the cognitive effects of cotinine in non-smokers. Sixteen subjects were tested on three doses of cotinine (0.5, 1.0, and 1.5 mg cotinine base/kg), and placebo, on a choice reaction time (RT) task and on a verbal recall task with short and long lists. Cotinine significantly impaired recall on the long list and displayed non-significant but generally consistent dose-related slowing of RT and N100 latency. The acute effects of cotinine were small, and probably do not account for the cognitive deficits observed in tobacco withdrawal, although the cognitive effects of chronic cotinine administration need to be investigated.

Key words Cotinine · Nicotine · Human information processing · Reaction time · Event related potentials · N100 latency · P300 latency

Introduction

Cotinine is the major proximate metabolite of nicotine (Gorrod and Jenner 1975; Benowitz and Jacob 1994). Cotinine blood levels average 250–300 ng/ml in cigarette smokers (Benowitz et al. 1983), exceeding nicotine concentrations by 15-fold. The elimination half-life of nicotine averages 2–3 h, although there is substantial variability between individuals (Benowitz et al. 1991, 1982), while the half-life of cotinine averages 15–19 h (Benowitz et al. 1983). The implication of the long half–life of cotinine is that smokers maintain high levels of cotinine in their bodies over 24 h of each day. Given such exposure to substantial concentrations of cotinine, it is possible that cotinine contributes to or interacts in some way with the effects of nicotine in smokers. Many studies have examined the effects of nicotine on information processing, but the effects of cotinine on information processing have not, to our knowledge, been reported.

A preliminary double-blind, crossover study was done with an oral dose of cotinine designed to produce levels similar to those found in smokers. Subjects were 13 non-smoking males. They were practiced on test procedures, then assigned to receive either placebo or 20 mg cotinine base (as the fumarate salt) on experimental days at least a week apart. On experimental days, subjects were tested before being given the drug or placebo and then retested at 1 and 2 h after dosing. Measures included a mood scale, vital signs, a memory task, and a visual choice reaction time task with associated ERP measures. The choice reaction time is referred to as the stimulus evaluation/response selection task (SE/RS). It combines two levels of stimulus complexity and two levels of response complexity so that results can be interpreted in terms of a serial information processing model. Reaction times, ERP latencies and their interactions with task variables have been shown to be differentially sensitive to a variety of pharmacological agents.

There were no drug effects on the mood scales, vital signs, memory tasks or P300 latencies. The N100 component of the ERP showed a significant drug by time by response interaction. Cotinine slowed N100 latencies for the hard response condition at 1 h post-drug and slowed N100 latencies for the easy response condition at 2 h. Finally, there was a suggestion of RT

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slowing in response to cotinine at 1 h. Levels of cotinine did not correlate significantly with any variables.

Higher order interactions are sometimes difficult to interpret, and even harder to evaluate when a variety of measures have been examined for changes. The small but suggestive effects seemed to merit a repeat study with larger doses of cotinine, which is the subject of the present report.

Materials and methods

Subjects

Sixteen healthy non-smokers were tested – eight male and eight female, ages 20–38. Subjects were recruited from a local university and were reimbursed for their participation. No subject had smoked more than five cigarettes in his or her lifetime and no subject had smoked any cigarettes within the past year. Subjects were excluded if they drank more than three cups of coffee or tea a day or more than six colas a day. (Subjects consumed their usual amount of caffeine on the morning of each test session and refrained from consuming alcohol for 48 h before each test session.) The protocol was approved by the UCSF Committee on Human Research, and all subjects gave written consent to participate.

Power was calculated using data from the pilot study. Considering slowing on the RT task as the primary measure and setting $\alpha = 0.05$, the study had an 80% power to detect a 37-ms slowing of RT relative to placebo. This effect is smaller than most we have observed from other depressant drugs, such as clonidine.

Design

Each subject was tested on four separate occasions – a practice session followed by three test sessions, each a week apart. On each test day, each subject was tested pre-drug and 1 h post-drug. The post-test was timed at 1 h based on results from the preliminary study.

A subgroup of eight subjects (four women, four men) was randomly assigned to receive doses of 0 (placebo) and 0.5 and 1.0 mg cotinine base (as the fumarate salt)/kg body weight; the other eight were to receive 0, 1.0, and 1.5 mg/kg body weight. This design was conceived to permit comparisons of 0 and 1.0 mg/kg doses in all subjects, while permitting the economical acquisition of additional dose/response information. Due to an error in interpreting the dosing code during drug preparation, nine subjects (five women, four men) actually received 0, 0.5, and 1.0 mg/kg, and the remaining seven received 0, 1.0, and 1.5 mg/kg doses. Doses were administered in capsule form. The order of drug administration was counterbalanced between subjects, and testing was double-blind.

Tasks

Stimulus evaluation/response selection (SERS)

A choice RT task (the "stimulus evaluation/response selection" or "SE/RS" task) was used that consists of two levels of stimulus complexity (which varies stimulus processing speed) and two levels of response complexity (varying response speed). For each trial in the task, the visual target appeared on a computer screen in one of four horizontally arrayed positions. Stimulus complexity was manipulated by varying the non-target items in the stimulus array to look more distinct (easy stimulus condition) or less distinct (hard stimulus condition) from the target stimulus. Response keys were horizontally arrayed like the stimulus display. In the easy response condition, the subject used either the right or left finger, pressing the rightmost key if the target appeared to the right of center screen and the leftmost key if the target appeared to the left of center. In the hard response condition, the subject used right and left index and middle fingers, pressing one of four keys corresponding to the exact position in which the target appeared.Conditions under which the SE/RS task was performed are described fully elsewhere (see, e.g., Brandeis et al. 1992; Halliday et al. 1994; Le Houezec et al. 1994). Each run of the task was completed in about 15 min.

Memory task

If cotinine has detrimental cognitive effects, we might expect to see an effect on learning and memory. Accordingly, a verbal free recall task was used that employed both "short" and "long" word lists.

A short list (15 words) was presented for recall four times (four trials) and a long list (30 words) was presented for four trials. To present the lists, each word appeared on the computer screen for 2 s, followed by 2 s of blank screen, then the next word appeared for 2 s, and so on. Subjects were required to complete a written recall following presentation of the entire list (with a time deadline of 90 s for the short list and 2 min, 15 s for the long list). By random assignment, half the subjects received a short list first every time, the other half received the long list first every time. For each of the two list lengths, all items were matched for number of syllables, frequency, and concreteness of meaning (source of words: Toglia et al. 1978). No items were repeated between lists. A different list was used for each test. Number of words recalled and number of intrusion words, incorrect words, and repetitions were scored on each trial.

Other dependent measures

Blood pressure and heart rate were taken, and the Profile of Mood State (POMS) (McNair et al. 1971) was administered. In addition, at the end of each test session the subject was asked his or her impression of the drug dose he or she had received during that session. The subject marked a vertical line on a visual analog scale. The scale was a 100 mm line, with the left end of the line labeled "weak" and the right end labeled "strong". The impression of dose scored was measured as the distance of the mark from the left end of the line, in centimeters.

Event-related potential recording

During each administration of the SE/RS task, EEG was recorded using a modification of the standard 10–20 system (Jasper 1958) recorded from 16 electrodes embedded in an electrode cap. ERP recording conditions are described in detail elsewhere (see, e.g., Brandeis et al. 1992; Halliday et al. 1994; Le Houezec et al. 1994).

Procedure

Blood pressure, heart rate, and self-ratings on the POMS were collected at the outset, just before administering the drug, and at 30, 60, and 75 min post-drug. The SE/RS procedure was performed at approximately 1 h post-drug. Saliva samples were collected pre-drug and at approximately 1.5 h post-drug. Salivary cotinine levels are known to be similar in magnitude and are highly correlated with plasma cotinine levels (Jarvis et al. 1984). Samples were assayed by gas chromatography, as described by Jacob et al. (1981), modified for use of a capillary column. At the end of each test session, the subject marked the visual analog scale question regarding his or her impression of the dose received.

Data analysis

Analyses were conducted using repeated measures analysis of variance (ANOVA). For the SERS task, within factors included drug, time (pre, post), stimulus complexity (easy, hard), and response complexity (easy, hard). Separate analyses were computed on RT, N100 and P300 latencies, and errors. Significance of the drug effect was tested by the drug by time interaction. Gender was a between-subjects factor. For the memory task, a repeated measures ANOVA was computed on number of words recalled (and errors). Within-subject factors included drug, time, and trial. Between-subject factors included gender and list order (short or long first). For all dependent variables, analyses were conducted on all subjects, comparing data for the placebo and 1.0 mg/kg dose. Separate analyses were done comparing 0, 0.5, and 1.0 mg/kg doses for the low dose subgroup ($n = 9$) and comparing 0, 1.0, and 1.5 mg/kg for the high dose subgroup ($n = 7$). Greenhouse-Geiser estimates of sphericity and adjusted P values were used for comparisons with more than one degree of freedom.

The correlation between saliva cotinine levels and memory task effect was examined. In addition, an analysis was done using the NONMEM (nonlinear mixed effects model) program (Beal and Sheiner 1990), specifically developed for analyzing population pharmacokinetic and pharmacodynamic data. A non-parametric spline function was used to fit the data.

Results

SERS task

Reaction time

Mean RTs (in ms) for all subjects ($n = 16$) at 0 versus 1.0 mg/kg for placebo were pre-test = 496(9) and post-test = 483(9), while for cotinine they were pre-test = 492(10) and post-test = 484(10). Figure 1 shows the differences in pre-post test RT for cotinine compared with placebo for the various treatment conditions. Cotinine "slowed" RT relative to placebo; that is, practice did not speed RT from pre to post to the same extent as with placebo. The effect was on average greater with larger doses compared to smaller doses of cotinine, but the differences were not statistically significant. There were no significant gender effects.

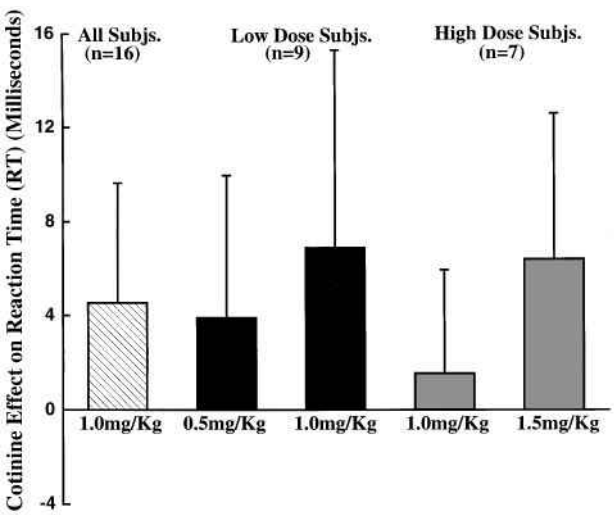

Fig. 1 Effects of cotinine on reaction time (RT). The size of the drug effect was calculated as the difference between the pre-post change in the drug condition and the pre-post change in the placebo condition. Positive values indicate slowing by the drug relative to placebo. Effects seen are not statistically significant

Accuracy

There were no significant changes in overall accuracy. The average proportion of errors for any drug condition or time did not exceed 5%.

N100

There were no significant drug effects on N100 latency. For the low dose subgroup, there was a near-significant tendency to slow N100 latency by the 1.0 mg/kg dose [$F(2,14) = 3.35$, $P < 0.09$]. Within each subgroup, the higher dose produced more slowing (or less speeding) than the lower dose, relative to placebo.

P300

There were no significant effects on P300 latency. As with RT and N100 latency results, within each subgroup the higher dose produced more slowing or less speeding than the lower dose, relative to placebo.

Memory task

Short list

For all subjects' 0 versus 1.0 mg/kg data on the 15-word list, there were no significant drug effects on the number of words recalled. There was a main effect of trial [$F(3,36) = 57$, $P < 0.0001$]; subjects increased the number of words recalled across the four trials (means were 9, 12, 13, and 14 words, respectively). There was no drug by time by trial effect; therefore, cotinine did not affect the learning rate. There was no effect of gender or order. Effects are depicted in Fig. 2. For all subjects combined, the 1.0 mg/kg dose decreased the number of words recalled. For the low dose subgroup, however, 0.5 mg/kg and 1.0 mg/kg doses increased the number of words recalled pre to post, relative to placebo. In the high dose subgroup, the 1.0 and 1.5 mg/kg doses decreased the number of words recalled relative to placebo. In each subgroup, the higher the dose, the fewer the number of words recalled.

Long list

For all subjects' 0 versus 1.0 mg/kg dose data on the 30–word list, cotinine significantly decreased the

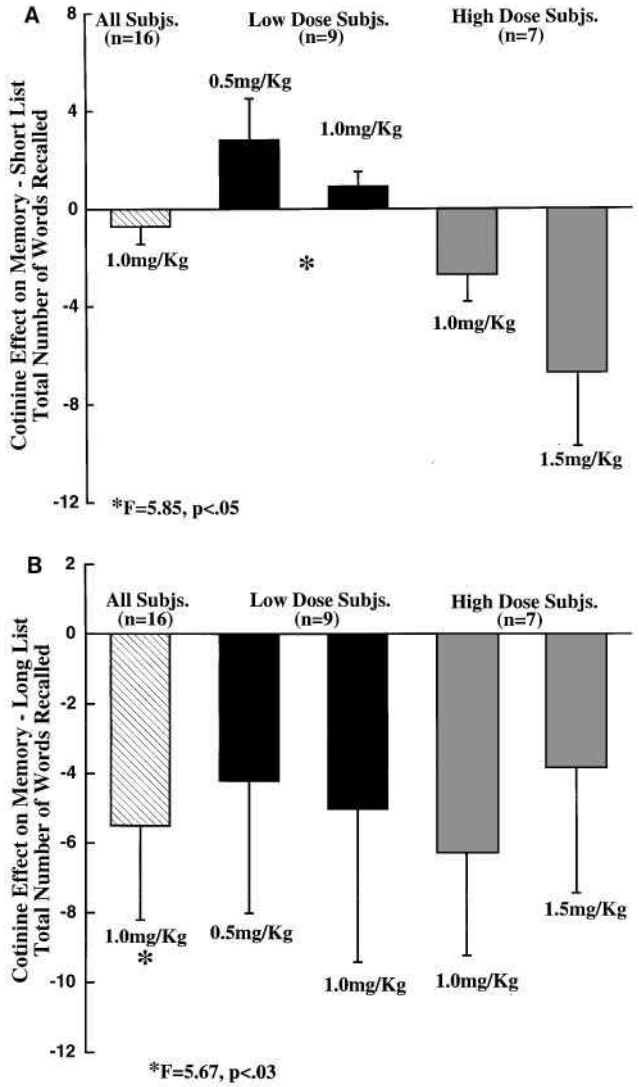

Fig. 2A, B Effects of cotinine on the memory task. **A** Results on the short (15-word) list; **B** results on the long (30-word) list. The size of the drug effect was calculated as the difference between the pre-post change in the drug condition and the pre-post change in placebo condition. Negative values indicate fewer words recalled for the drug relative to placebo; positive values indicate more words recalled for drug versus placebo

number of words recalled (on average, 5.5 fewer words, pre to post, relative to placebo, over the four trials) [Drug by time interaction yielded $F(1, 12) = 5.67$, $P < 0.03$]. There was a main effect of trial [$F(3, 36) = 134$, $P < 0.0001$]. Subjects improved across trials (means = 14, 20, 24, and 26 words, respectively). None of the other interactions with drug was significant. There were no effects of gender or order. For the dose subgroups, there were no significant drug effects. Effects are depicted in Fig. 2. For the long list, all drug effects were consistent across subgroups and doses in decreasing the number of words recalled, relative to placebo.

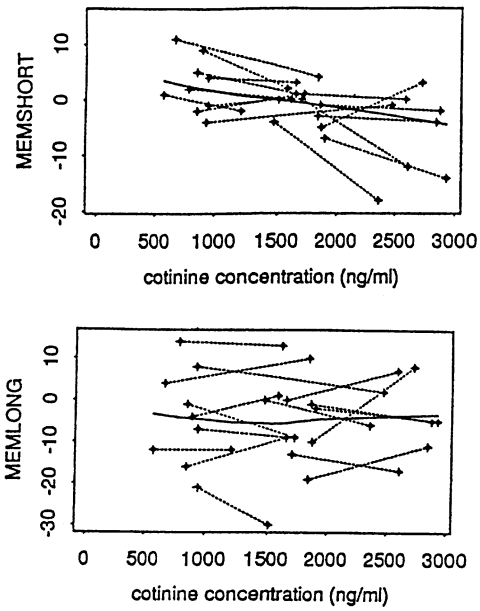

Fig. 3 Relationship between saliva cotinine levels and pair of memory task effects (difference between pre-post change with placebo and pre-post change with cotinine for each of two doses) for the short and long lists, using a spline fitting routine in the NONMEM program. Each subject is represented by a *connected pair of points*, corresponding to each subject's pair of cotinine doses

Blood pressure/heart rate/POMS

Cotinine had no significant effects on blood pressure or heart rate at any dose. Neither did it affect any of the six POMS subscales (tension, anger, depression, vigor, fatigue, or confusion).

Subjective impression of dose

One score of each subject's subjective impression of the strength of dose received was obtained for each test session. That score (number of centimeters from 0 on a 10 cm line) did not correlate with actual dose received ($r = 0.2$, $P < 0.16$), although it did correlate significantly with session number ($r = 0.33$, $P < 0.02$). Mean score increased as session number increased [means = 1.18 (1.2), 2.29 (20), and 3.12 (3.3) for sessions 1–3, respectively].

Saliva cotinine

Pretest saliva cotinine levels for all subjects verified their non-smoking status. Post-test saliva cotinine confirmed that 15 of the 16 subjects were administered the expected doses, according to their random assignment. For one subject, saliva cotinine levels indicated that she had received 0, 0.5, and 1.0 mg/kg doses instead of her assigned 0, 1.0, and 1.5 mg/kg doses.

Mean post-test saliva levels were as follows: placebo = 3(2) ng/ml; 0.5 mg/kg dose = 826 (130) ng/ml; 1.0 mg/kg dose = 1720(268) ng/ml; and 1.5 mg/kg dose = 2745(140) ng/ml.

Saliva cotinine levels across all subjects showed a significant inverse correlation with the memory task effect for the short list, such that the number of words recalled decreased as the level of cotinine increased ($r = -0.54$, $P < 0.001$). There was no such correlation for the long list ($r = 0.03$, $P > 0.8$). As with the correlational analysis, with the NONMEM analysis saliva cotinine was found to have a significant linear (decreasing) relationship to memory effects on the short list, but no significant relationship to memory effects on the long list. Figure 3 illustrates these results. Saliva cotinine was not found to have a significant relationship to RT effects.

Discussion

Taken as a whole, the data suggest that acute oral cotinine may have some mild depressant actions. The slowing of N100 latencies in the preliminary study was not replicated in the second study, while memory effects seen in the main study were not seen in the preliminary study. Vital signs were unchanged and subjects could not identify the active drug subjectively. Nevertheless, there was a consistent trend for RT and N100 to be slowed and for memory to be impaired in a dose–related fashion.

The doses of cotinine administered in our study were quite large, with resultant plasma cotinine concentrations 5–10 times those seen in regular smokers. The use of high doses with only small effects on cognitive function indicates that cotinine is much less potent than nicotine. Cotinine has been shown to have behavioral effects in animals, but here, too, cotinine was much less potent than nicotine (Risner et al. 1985; Goldberg et al. 1989; Takada et al. 1989).

Cognitive testing was performed at 1 h after oral cotinine doses. The time of peak cotinine concentration in the plasma after oral dosing averages 45 min (DeSchepper et al. 1987). Cotinine is a more polar molecule than nicotine, so it is possible that there is a delay between peak plasma and peak brain levels of cotinine. A positron emission tomography study of the uptake of intravenous racemic (^{11}C) cotinine in the human brain revealed a low level of uptake, but that level of uptake was seen within 10 min of dosing (Halldin et al. 1992). It is possible that testing in 1 h after oral cotinine dosing might miss the maximal pharmacologic effect. Of note, however, is that the preliminary studies, with measurement of the SE/RS at both 1 and 2 h after oral cotinine, found no significant difference between responses at these times, suggesting that sampling at 1 h is adequate (although we cannot exclude a maximal effect occurring later than 2 h).

The memory effect was most notable in the long list recall. If one wished to argue that cotinine contributes to the memory problems relieved by nicotine in smokers, one could note the work by Rusted and Eaton-Williams (1991), who argue that attentional demands of the task (tested by longer list) are more responsible for sensitivity to nicotine than memory per se. One could argue that cotinine also primarily affects sustained attention, although by impairing rather than facilitating it. However, there was no significant interaction of cotinine with trial for either list. If cotinine affected sustained attention, one would expect to see a greater effect on trial 4. Thus, an effect on memory per se cannot be ruled out.

Figure 2 illustrates the dose-related effects on the short list; improvement of recall at 0.5 mg/kg, less improvement from 0.5 to 1.0 mg/kg in the low dose subgroup, impairment from 1.0 mg/kg in the high dose subgroup, and the most impairment at the 1.5 mg/kg dose. In contrast, for the long list, as illustrated in Fig. 2, all doses apparently impaired recall, although the effect was greatest at 1.0 mg/kg. The correlational and NONMEM analyses showed cotinine effects to be significantly inversely related to saliva cotinine levels for the short list, but not the long list. For the long list, the dose effect was not linear; the impairment seen at all doses bottomed out at the 1.0 mg/kg dose. The long list would also have created more variability because, as memory requirements increased, individual differences in memory abilities and strategies would have been more likely to hide drug effects. Only at 1.0 mg/kg (where the sample size was also largest) was the drug effect larger than the individual differences, hence, the significant ANOVA result for that dose.

It appears from our findings that cotinine has either a general attentional or some specific effect on recall memory. Slowing effects of cotinine on information processing, however, appear to be smaller than the effects on information processing we have seen with other drugs. Also, in contrast to other drugs (including nicotine, for example; see Le Houezec et al. 1994), subjects given cotinine showed no subjective awareness of having received a drug.

Snyder and Henningfield (1989) and Snyder et al. (1989) reported robust slowing of RTs following 12 and 24–48 h of smoking deprivation. Smokers consistently report loss of concentration after cigarette deprivation (Hughes et al. 1990). Conceivably, the depressant action of cotinine, unopposed by the stimulant actions of nicotine, could contribute to such withdrawal symptoms. The small magnitude of effect in our study suggests that cotinine alone does not account for such pronounced withdrawal effects. It should be noted that Keenan et al. (1994) found mood effects associated with intravenous cotinine infusions in abstinent cigarette smokers, although these mood effects tended to be more

stimulant in nature than the depressant effects suggested by our data. In any case, both our work and that of Keenan suggest that cotinine has psychoactivity that could play some role in nicotine addiction. Our study of the acute effects of cotinine in non-smokers does not exclude the possibility of a greater effect of cotinine with chronic administration or in smokers. The possible psychoactivity of cotinine with chronic exposure and in smokers after smoking cessation deserves further investigation.

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