an intense morphine response. All four subjects with medial thalamic lesions became somnolent (Figs. 1F and 2F), and the righting response disappeared. These effects were absent in animals with caudate and hippocampal lesions.

While medial thalamic lesions had little, if any, effect on precipitated withdrawal effects of the morphine antagonist naloxone, these lesions had a drastic effect on sensitivity to morphine in tolerant rats. It is difficult to reconcile these results with the view that tolerance to morphine is a generalized phenomenon occurring throughout the central nervous system. If this were the case, lesions in different parts of the brain should be equally ineffective in altering morphine sensitivity in tolerant subjects. Kerr and Pozuelo (*7*) demonstrated that lesions of the ventromedial nucleus of the hypothalamus and, to a lesser extent, lesions of the septal nucleus of tolerant rats resulted in increased sensitivity to morphine. Since behavioral criteria were used in their experiments to assess tolerance, whereas EEG criteria were used in the present study, it is not possible to compare the magnitude of the effects of lesions in the two studies.

Because of the many complicated ways brain lesions and drugs interact, it would be imprudent to provide neuroanatomical speculation as to why lesions of the septum, hypothalamus, and medial thalamus should alter morphine sensitivity in tolerant rats. For example, localized lesions of one region can lead to a concomitant alteration in levels of neurotransmitters in distant regions of the brain (*8*). This effect is accompanied by an alteration of response to barbiturate anesthesia (*8*). Since morphine induces changes in central cholinergic metabolism (*9*), it would be useful to determine how medial thalamic, septal, and hypothalamic lesions affect this cholinergic response to morphine.

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10. Supported in part by the U.S. Army Medical Research and Development Command under D. A. Project 3A-062 110A833, and the Office of Naval Research contract NR201-037.

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Amphetamine Effects in Man: Paradoxical Drowsiness and Lowered Electrical Brain Activity (CNV)

Abstract. *Thirteen of 20 normal adults given 10 milligrams of dextroamphetamine exhibited paradoxical drowsiness accompanied by lowered electrical brain activity (contingent negative variation, or CNV) in the first hour post-drug. During this period, seven subjects showed behavioral alertness and increased CNV amplitude. Both groups of subjects showed heightened alertness 2 and 3 hours post-drug. Amphetamine is not a simple stimulant of the central nervous system but can also act as a depressant.*

Amphetamine is a stimulant of the central nervous system which has been widely used both clinically and socially. As therapeutic medication, it has been employed with some success in the treatment of obesity, hyperactivity in children, and narcolepsy (*1*). On the other hand, prolonged use has resulted in amphetamine psychoses, which are similar to paranoid schizophrenia and which have been associated with homicide (*2*). One hypothesis is that chronic amphetamine use stimulates arousal processes of the central and peripheral nervous systems and that overstimulation leads to overarousal, a disruption in attention, and psychotic behavior (*3*). This view is supported by findings that amphetamine increases behavioral arousal, exerts alerting effects on electroencephalographic activity, and increases brain norepinephrine levels (*4*). Therefore, we attempted to demonstrate in normal humans that amphetamine increases the amplitude of an event-related electrical brain wave called "contingent negative variation" (CNV) (*5*), which is an indicator of alertness (*6*). Unexpectedly, the drug produced a transient state of drowsiness and reduced CNV amplitude.

Subjects were 20 paid volunteers (*7*). The first experimental session was to acclimatize subjects to testing procedures. Drug or placebo was given in the second and third sessions, which were separated by 5 to 11 days. Subjects were randomly assigned to two groups of ten subjects each. One group received amphetamine first and placebo second. The second group received placebo first and amphetamine second. Neither subject nor experimenter knew the substance of the tablets (double blind procedure).

The experimental task consisted of a constant-foreperiod, simple reaction-time paradigm. The preparatory stimulus (first stimulus or S_1) was a brief (10-μsec) flash of dim light presented 1 m from the subject's eyes through a 2.5 cm aperture. The second stimulus (S_2) was a 1000-hz tone at a sound pressure level of 70 db (relative to 0.0002 dyne/cm^2) presented 1.5 seconds after the light flash and terminated by a telegraph key press. Intertrial intervals varied randomly from 13.5 to 21.5 seconds.

Experimental sessions began at approximately 9 a.m. A control (pretreatment) run consisted of 16 trials of S_1–S_2–motor response (light–tone–key press) and lasted 5 minutes. Either 10 mg of dextroamphetamine (two 5-mg tablets) or identical placebo tablets were administered orally. Eighteen runs with intervening rest periods (5 minutes) were given for 3 hours post-treatment.

Electroencephalographic (EEG) recordings were made from silver–silver chloride electrodes attached to vertex (Cz) and joined mastoid processes. Vertical eye movements were monitored by an electrooculogram (EOG) recorded from above and below the right eye (*8*).

The evaluation of amphetamine effects on CNV amplitude was complicated by an unexpected finding of drowsy behavior among the majority

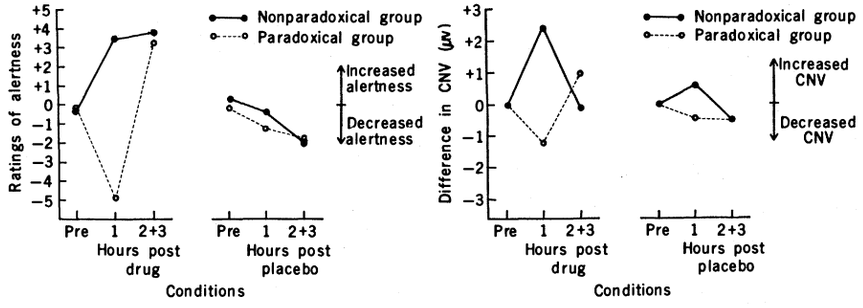

Fig. 1. The left half of the figure shows ratings of behavioral alertness for groups of paradoxical ($n = 13$) and nonparadoxical ($n = 7$) subjects before and after amphetamine and placebo. The right half of the figure shows adjusted differences in CNV amplitude. The similarity in patterns of behavioral alertness scores and CNV amplitude changes can be seen for paradoxical and nonparadoxical groups in the first hour post-drug.

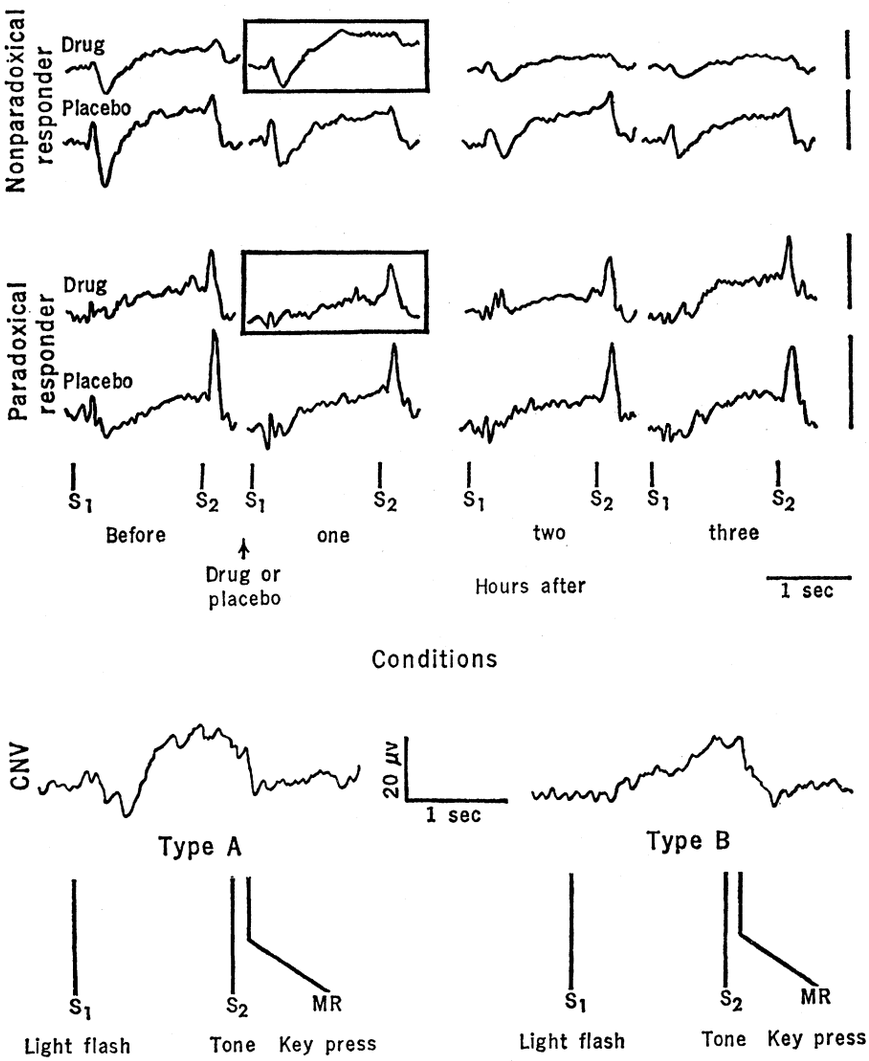

Fig. 2. (Upper part) Different patterns of CNV changes for two individuals who differ in behavioral response to amphetamine. The nonparadoxical responder, who exhibited behavioral alertness in the first hour post-drug, showed elevated CNV amplitude at this time (see boxed wave). The paradoxical responder, who became drowsy in the first hour post-drug, showed reduced CNV amplitude at this time (see boxed wave). The four vertical lines at the right represent calibration signals of 25 μv. (Lower part) Two types of CNV shape based on a fast rise time to maximum amplitude (type A) and a gradual rise time (type B). The paradoxical group of amphetamine responders, who showed early drowsiness post-drug, generally showed type B CNV's in the control (pre-treatment) situations. Nonparadoxical responders, who showed behavioral alertness 1 hour after amphetamine administration, characteristically showed type A CNV's.

(65 percent) of subjects in the first hour post-drug. These individuals displayed droopy eyelids and dozed off during testing. In rest periods, they verbalized feelings of sleepiness and an inability to keep their eyes open (*9*). Other individuals, on the other hand, exhibited clear behavioral alertness (for example, eyes wide open) and verbalized feelings of excitement and euphoria (*10*). The 13 subjects who received negative scores (low alertness) for the first hour post-drug were classified as "paradoxical responders." The seven subjects who received positive scores (high alertness) were classified as "nonparadoxical responders" (*11*). Ratings of behavioral alertness of the two groups for amphetamine and placebo sessions appear in the left side of Fig. 1 (*12*).

The nonparadoxical responder group showed an increase ($P < .05$) in mean alertness scores in the first hour post-drug compared to the pre-drug level, whereas the paradoxical responder groups showed a decrease ($P < .01$) (*13*). Amphetamine produced a similar change in CNV amplitude, as is shown in the right side of Fig. 1 (*14*). The nonparadoxical group showed an increase ($P < .05$) in mean CNV amplitude in the first hour post-drug compared to pre-drug, whereas the paradoxical group showed a (nonsignificant) decrease. This latter decrease for the paradoxical group is significantly different ($P < .01$) from the increase in CNV amplitude shown by the nonparadoxical group in the first hour post-drug (*15*). The upper part of Fig. 2 shows examples of CNV changes for nonparadoxical and paradoxical individuals.

A classification of subjects on the basis of CNV shape with a fast rise time (type A in the lower part of Fig. 2) or a gradual rise time (type B) showed a greater incidence of type B CNV's among the 13 paradoxical subjects (4 A's and 9 B's) compared with the nonparadoxical subjects (6 A's and 1 B) ($\chi^2 = 3.61$; $P < .06$) (*16*).

In conclusion, amphetamine produced dissimilar patterns of brain-behavior response in two groups of normal adults, that of paradoxical drowsiness in the first hour post-drug accompanied by reduced electrical brain activity (reduced CNV amplitude) in one group and that of behavioral alertness associated with increased CNV amplitude in another group. Consequently, amphetamine is not a simple stimulant of the central nervous

system and can produce an early, transient depression in brain activity (*17*). The use of amphetamine as an antifatigue agent in sedentary situations resembling that of the laboratory (for example, sustained motor vehicle operation) can produce a dangerous, transient lethargy, particularly among individuals characterized by CNV's having a slow rise time (type B in Fig. 2). That the paradoxical drowsiness we observed was accompanied by depressed brain activity and subjective reports of a dysphoric mood indicates that principles of psychopharmacology based on amphetamine being solely a centrally acting stimulant drug require review.

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7. All subjects were females between the ages of 18 and 35 (median, 21) and were judged by a psychiatrist to be in good physical and mental health and free of drugs.
8. The time constant for EEG and EOG recordings was 8.2 seconds. High frequency cut-off was 75 hz (50 percent amplitude reduction) with a 12 db per octave roll-off. Trials with eye movements (including eye blinks) and key presses in the S_1–S_2 interval were omitted in off-line averaging. Averaged CNV's were based on 6 to 12 trials per run, the number being constant for a given individual. CNV amplitude was the difference in average voltage between the 512-msec period pre-S_1 and the 256-msec period pre-S_2.
9. In the first hour post-drug, four subjects also verbalized dysphoric mood (for example, "the saddest I ever felt" and "very very blue"). Two individuals displayed tears in their eyes.
10. Ratings were made on a six-point scale for test behavior (5-minute run) and verbalizations made during 5-minute rest intervals: +3, very high ("excited," "euphoric," laughing, and glassy eyes); +2, high ("very alert," "wide awake," and frequent smiling); +1, moderate ("alert" and "awake"); −1, low ("bored" and "tired"); −2, very low ("very tired," head to side, and droopy eyelids); −3, extremely low ("sleepy," "cannot keep eyes open," sleeplike nodding, and eyes closed). The occurrence of more than one indicator of change in alertness resulted in a cumulative rating, for example, a rating of "+5" resulted from the appearance of glassy eyes (+3) *and* the verbalization of feeling "very alert" (+2).
11. Mean ratings on this criterion variable were: −4.85 (range: −1 to −8) for the paradoxical group and +3.29 (range: +1 to +5) for the nonparadoxical group.
12. Means (and standard deviations) of behavioral alertness rating scores in the left half of Fig. 1 for pre-treatment, 1 hour post-treatment, and 2 and 3 hours (combined) post-treatment are as follows: (i) nonparadoxical-drug: −0.29 (0.76), +3.29 (3.45), and +3.79 (2.93); (ii) paradoxical-drug: −0.15 ((0.80), −4.85 (3.31), and +3.19 (2.98); (iii) nonparadoxical-placebo: +0.29 (0.76), −0.43 (0.98), and −1.86 (1.50); (iv) paradoxical-placebo: −0.08 (1.04), −1.08 (0.95), and −1.62 (1.58).
13. All mean differences were evaluated by analysis of variance of simple effects and *t*-tests. Since these two techniques yielded comparable results, the simpler procedure—that of *t*-tests—is presented here. All *P* levels are two-tail values.
14. Means (and standard deviations) of CNV amplitude (μv) for pre-treatment, 1 hour post-treatment, and 2 and 3 hours (combined) post-treatment are as follows: (i) nonparadoxical-drug: 10.84 (2.72), 12.94 (2.56), and 9.90 (3.50); (ii) paradoxical-drug: 13.63 (3.98), 10.87 (4.43), and 13.16 (4.27); (iii) nonparadoxical-placebo: 13.63 (3.27), 12.72 (4.30), and 11.68 (3.71); and (iv) paradoxical-placebo: 13.82 (4.68), 11.73 (3.42), and 11.78 (3.54). The mean pre-drug CNV amplitude was higher for the paradoxical group (13.63 μv) than for the nonparadoxical group (10.84 μv) ($F = 4.49$; d.f. = 1, 18; $P < .05$). Consequently, all raw scores (CNV amplitude in microvolts) were adjusted to remove interindividual variability among subjects in pre-drug and pre-placebo levels [see J. J. Tecce and J. O. Cole, *Psychopharmacologia* **24**, 159 (1972)]. These Adjusted Differences Scores are presented in the right half of Fig. 1 and are the basis of statistical tests. As shown in Fig. 1, a positive value indicates an increase in CNV amplitude after treatment compared to pre-treatment level, whereas a negative value indicates a relative decrease.
15. In the second and third hours post-drug (combined), means of alertness scores were increased ($P < .01$) for both paradoxical and nonparadoxical groups. In the placebo session, both groups showed significant reduction ($P < .05$) in mean behavioral alertness in the second and third hours (combined) post-placebo. No CNV changes were significant in the placebo session. As can be seen in the right side of Fig. 1, the increase in CNV amplitude for the nonparadoxical group in the first hour post-drug disappeared in the second and third hours. During these latter hours, there were reports of cognitive surges ("racing thoughts" and "endless ideas"), which are possible sources of distraction and disruption in CNV development.
16. The classification of each individual's pre-treatment CNV shape as type A or B [J. J. Tecce, *Arch. Gen. Psychiatry* **24**, 1 (1971)] was made by a consensus of two judges who were blind to the experimental conditions.
17. Normal and paradoxical responders do not differ in age, height, weight, use of birth control pills, point in time tested within the menstrual cycle, or time of day amphetamine was ingested (average times for ingestion by nonparadoxical and paradoxical groups were 10:56 and 11:03 a.m., respectively). These groups may differ in rate of drug absorption from the gastrointestinal tract to the circulatory system. The two groups did not differ in amount of sleep reported for the night before testing or in amount of breakfast taken the morning of testing (subjects were asked to keep to their normal sleep hours and breakfasts).
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D(−)-Lactic Acid and D(−)-Lactate Dehydrogenase in Octopus Spermatozoa

Abstract. *The spermatozoa of* Octopus dofleini martini *produce anaerobically* D(−)*-lactic acid and possess a very active* D(−)*-lactate dehydrogenase. In this respect, while resembling certain microorganisms, they differ strikingly from mammalian spermatozoa which produce* L(+)*-lactic acid and contain* L(+)*-lactate dehydrogenase.*

The anaerobic survival and motility of spermatozoa are both strictly dependent on the availability of carbohydrates that can undergo glycolysis. Mammalian spermatozoa depend largely on extracellular carbohydrate, chiefly fructose, provided by the male accessory secretions; the intracellular glycogen content of mammalian spermatozoa is notoriously low and they lack some of the enzymes necessary for glycogenolysis (*1*). On the other hand, in the spermatozoa of certain other animals, particularly in some invertebrates, a different situation is encountered. A notable example is provided by the spermatozoa of the giant octopus of the North Pacific, *Octopus dofleini martini*. In this animal, the spermatozoa are characterized by the presence of a large reserve of intracellular glycogen, and in addition, they possess the enzymes required for glycogenolysis, including phosphorylase and phosphoglucomutase (*2*).

The spermatozoa of *O. dofleini martini* are capable of long survival both in vitro and in vivo. When suspended in seawater and incubated anaerobically at 10°C, that is, at a temperature close to that of the animal's normal habitat in the North Pacific, these spermatozoa retain their motility for several days. In the present study we investigated the metabolism of sperm suspensions incubated anaerobically in vitro, and we have identified lactic acid as a major metabolite, using the following three chemical methods: (i) colorimetric, by means of the hydroxydiphenyl reagent (*3*); (ii) iodometric, by distilling the acetaldehyde formed by oxidation with potassium permanganate in the Lieb-Zacherl apparatus and by determining the acetaldehyde bound to sodium hydrogen sulfite by titration