The effects of caffeine on physiological functions and mental performance

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Summary. Polygraphic monitoring of several physiological variables was done throughout an experiment investigating the effects of caffeine on mental performance. The experiment started with a mental maze learning task. Then the subjects were given the test beverages according to the group design (CC group (N = 16): 300 mg caffeine in decaffeinated coffee, DC group (N = 16): decaffeinated coffee, WW group (N = 8): warm water, and NB group (N = 8): no beverage). The experiment continued with a letter cancellation task which was followed by a second mental maze learning task. The caffeine treated subjects differed from the other groups by increased regularity of letter cancellation performance, as indicated by decreases in intraindividual variance. They also differed from the other groups by a slight but significant acrodermal vasoconstriction. No intergroup differences were obtained for mental maze learning, heart rate, respiration, muscle tension, and skin conductance. The results suggest therefore that the drug at this dose level improves behavioral routine and speed rather than cognitive functions and that the vegetative side effects are minimal.
Key words. Caffeine; mental maze; letter cancellation; vasoconstriction; psychophysiology.

The widespread consumption of coffee in the absence of a clear definition of the physiological and behavioral spectrum of action has continued to stimulate research[16]. Unfortunately, due to the complexity of the pharmacology of caffeine, the possibility of effects of other, as yet unidentified active substances in coffee, and putative interactions with personality, physical health, history of the use of caffeine either alone or in combination with other drugs, etc., much of the research done so far has produced results that are inconsistent or ambiguous[9,11]. The present experiment was designed to evaluate simultaneously a) mental maze learning as a cognitive test of 'intellectual performance', b) letter cancellation as a test of 'routine, speed, and endurance', and c) the development of a set of polygraphically recorded psychophysiological parameters.

The results of studies on cognitive functions are particularly ambiguous[9,11,16]. The large catalogue of tasks used in these studies includes verbal learning[2,6,13,14,24,25], verbal memory[2,6,17,21], different subsets of intelligence tasks or thinking[14,23], numerical learning[15,22,25], tactile and auditory learning[18,25], etc. Particularly interesting, therefore, are studies which tried to assess caffeinic action across different types of tests in attempts to clarify the task-specificity of the effects. Nash[25], who used a particularly wide battery of tests, found for some significant improvement and for others only a tendency toward improvement. Improvement was noted for immediate recall of auditory or verbal stimuli and for associative productivity but not for visual thinking. Lienert and Huber[22], who compared caffeinic action across subsets of an intelligence test, came to the conclusion that caffeine improved performance for subsets requiring intellectual speed rather than for subsets requiring intellectual power. For the present experiment, a mental maze task was used which requires primarily cognitive spatial concept formation.

Mental performance requiring speed, endurance, or vigilance was more consistently reported to benefit from caffeinic influence than were cognitive functions[10,16,34]. Letter cancellation, the test used in the present experiment, was carried out under the pressure of performance reward. In order to obtain a continuous measure of performance and intraindividual variance, the subjects had to start a new row on the test sheets for each 20 s of the 30-min testing period. Interest in the cardiovascular effects of caffeine has been renewed in the light of the recent controversy as to whether coffee consumption might be associated with increased risks for coronary heart disease[7,19,26]. In the present experiment heart rate and finger pulse amplitudes were continuously registered along with frontal muscle tension, respiration, and changes in skin conductance.

Method

Subjects. 48 healthy male subjects were selected from respondents to a newspaper advertisement (average age 27 years, body height 177 cm, b.wt 67 kg, self-reported coffee consumption two cups/day). 18 subjects were light smokers. None were alcohol abstainers. Before the experiment they were required to abstain from caffeine consumption (foodstuffs, beverages, medicaments) for a period of 17.5 h starting at midnight the day of testing. For their participation they received SFr. 12.–/h, which was supplemented by premiums for performance in the d2 letter cancellation test.

Mental tasks

a) Conceptual learning (mental maze): The subjects were seated in a soundproof cabin in front of a screen and a response panel with 49 identical keys arranged in a square 7 × 7 matrix. The task consisted in finding out by trial and error which of the keys produced 'reward' by the appearance of a landscape picture on the screen and which of the keys produced 'no reward' by the appearance of a solid black surface on the screen. Different mazes, i.e. corresponding configurations of correct keys, were used. For 'training' trials they consisted of simple bars and for Maze I, presented before the experimental treament, and Maze II, presented after the experimental treatment, of two different bisymmetrical, rather complex arrangements which were matched in a previous pilot experiment for similar learning difficulty[31]. For each configuration the subjects were al-

lowed 5 min per trial or the time needed to find all correct keys, whichever occurred first. Trials were separated by 3-min intervals.
b) d2 Letter cancellation test[4]: The test sheets contained 14 rows each with 47 d's, all marked above and/or below with up to four apostrophes in a random sequence. The task consisted in crossing out each d which had two apostrophes. A new row was begun every 20 s at a command signal (1000-Hz tone for 1 s).

Psychophysiological recording

Two Beckman electrodes (Ag/AgCl, 0.5 cm^2 active surface) were placed on the chest (ECG recording), two medially below the ankle of one leg (SCC recording), two on the lower forehead (EMG recording), and one on the upper forehead (common reference). Respiratory signals were obtained from a strain gauge belt fixed around the chest and the pulse amplitudes by fixing a miniature infrared transducer[28,32] to the tip of the index finger of the nondominant hand. The system Messerschmidt Bölkow (series 3800) was used for preamplification, a Beckman polygraph for graphic display, an oscilloscope for EMG monitoring, a PCM system for digitalization of the signals (Johne & Reilhofer, Type 8K10, 8 channels), and a modified tape recorder (Stellavox SP-7) for storing the PCM signals on magnetic tape. All equipment was located outside the testing cabin, and the experimenter supervised the subjects by remote video surveillance.

Testing procedure

All individual experimental sessions started at 17.30 h and were carried out according to the following time protocol:
- Taking a 1-ml saliva sample and freezing it for later caffeine analysis (HPLC method[20], carried out by courtesy of Prof. Ch. Schlatter, Institute of Toxicology, ETH, Zürich).
- Fitting and testing the electrodes and transducers. System test and start of recording.
- Presentation of the mental maze training configurations for 15 min.
- Mental Maze I learning for 30 min, starting with the first trial.
- Drinking the test beverage within 1 min.
- d2 Letter cancellation test for 30 min, divided for later statistical analysis into six parts of equal length.
- Mental Maze II learning for 30 min.
- Taking a second saliva sample and removing the electrodes. Filling in questionnaires about personality, FPI (Freiburger Persönlichkeitsinventar[12]), and for self-reported caffeine and drug consumption.

Treatments

As their single experimental treatment eight subjects received no beverage (NB), eight subjects received 100 ml warm water (WW), 16 subjects received 100 ml decaffeinated coffee (DC), and 16 subjects received the same amount of decaffeinated coffee with 300 mg pure caffeine (Fluka AG, Buchs, Switzerland) added (CC).

Data analysis

The data pool for statistical analysis included: a) Mental Mazes I and II: Time spent and number of correct and incorrect key responses per trial. b) d2 Letter cancellation test: Total performance and variance of performance across the successive 20-s periods of each of the six successive 5-min test periods. c) Psychophysiological recordings: Averages and variances of peak frequencies (except for pulse amplitudes) and peak amplitudes (except for heart rate) for each successive 10-s period and for each recording channel. These values were further averaged individually for each period of the testing protocol and tested by regression analysis for possible time trends within each testing period.
The statistical procedure involved as a first step a set of discriminant analyses (stepwise procedure BMDP7M) across the entire data pool of each testing phase in order to test for intergroup differences. All physiological data were thereby standardized as percentages of the values obtained for the intertrial intervals of the initially presented training mazes. Subsequent univariate procedures (SPSS system) involved the application of ANOVA and test-retest reliability tests (Kendall correlations) to the measures of Maze I and Maze II performance and the application of multiple two-tailed t-tests to the letter cancellation and psychophysiological data. A crosscorrelational analysis (Kendall coefficients) across all data items concluded the statistical analysis.

Results

No significant intergroup differences for age, body weight and height, self-reported coffee consumption, and FPI personality scores were obtained by discriminant analysis. Further, all these values were within the limits of standards.
Saliva caffeine concentrations were low (0.14–0.24 ppm) for all preapplication samples. They were elevated 1 h postapplication for the CC group only (3.71 ± 1.2 ppm) and remained at nearly the same level for a few additional samples taken from this group 2 h postapplication.
In figure 1 the mental maze learning and the letter cancellation data for the four groups are plotted across the successive periods of the task program. With the two mazes time to criterion and errors to criterion improved from trial to trial ($p < 0.01$ for the trial factors in repeated measure ANOVA's) without any significant intergroup differences. Correct letter cancellation performance improved gradually for all groups and approached a ceiling towards the end of the test. In the CC group only variance across the successive lines of the test sheets decreased, with the differences against the other groups except the NB group reaching significance for the second half of the test (Wilcoxon two-tailed, $p < 0.01/0.02$).
The development of the physiological measures across the entire experiment is shown in figure 2 for the R-R intervals of the ECG, for the pulse amplitudes, and for EMG power. Table 1 shows the results of the discrimi-

nant analysis which was applied separately to each successive test phase. No significant intergroup differences were obtained for any of the preapplication test periods but they were found for each of the postapplication periods (criterion $F > 4.0$). The slight but consistent vasoconstriction seen in figure 2 turned out to be the variable consistently separating the four groups (plethysmographic amplitudes), and the frequency of correct classification was consistently highest for the CC group, reaching levels around 80% (table).

A closer look at the development of the different variables across time (fig. 2) reveals that heart frequency was the only variable to be affected by the program of the different mental tasks. Compared with the initial baseline values, the heart rate intervals decreased for the trial periods of Maze I and particularly for the letter cancellation periods but returned to values within the control range for Maze II.

The pulse amplitudes were unaffected by the program of the mental tasks. The apparently high values obtained for the WW group were due to aberrant behavior in a few individuals. On the other hand, the consistent slight vasoconstriction seen in the CC group was accompanied by only a modest degree of variance, and t-test significance was reached for both the trial and intertrial intervals of Maze II against the two groups WW and DC but not against NB. Furthermore, time trends calculated within the individuals revealed a consistent picture in the CC group only. In this group gradual

Percent of correct group classifications and discriminating variables obtained by discriminant analysis

Testing phase	Treatment groups CC	DC	WW	NB	All groups	Discriminating variable*	F-value
d2 test 1st third	56.3	6.3	50.0	12.5	31.5	PLET$\bar{x}$	4.2548
d2 test 2nd third	81.3	25.0	37.5	12.5	43.8	PLET$\bar{x}$	4.3861
d2 test 3rd third	80.0	31.3	37.5	12.5	44.7	PLET$\bar{x}$	5.5498
Maze II trials	81.3	12.5	50.0	12.5	41.7	PLET$\bar{x}$	4.5218
Maze II intertrial intervals	62.5	43.8	37.5	0.0	41.7	PLET$\bar{x}$	4.200

*PLET$\bar{x}$ = average pulse amplitudes.

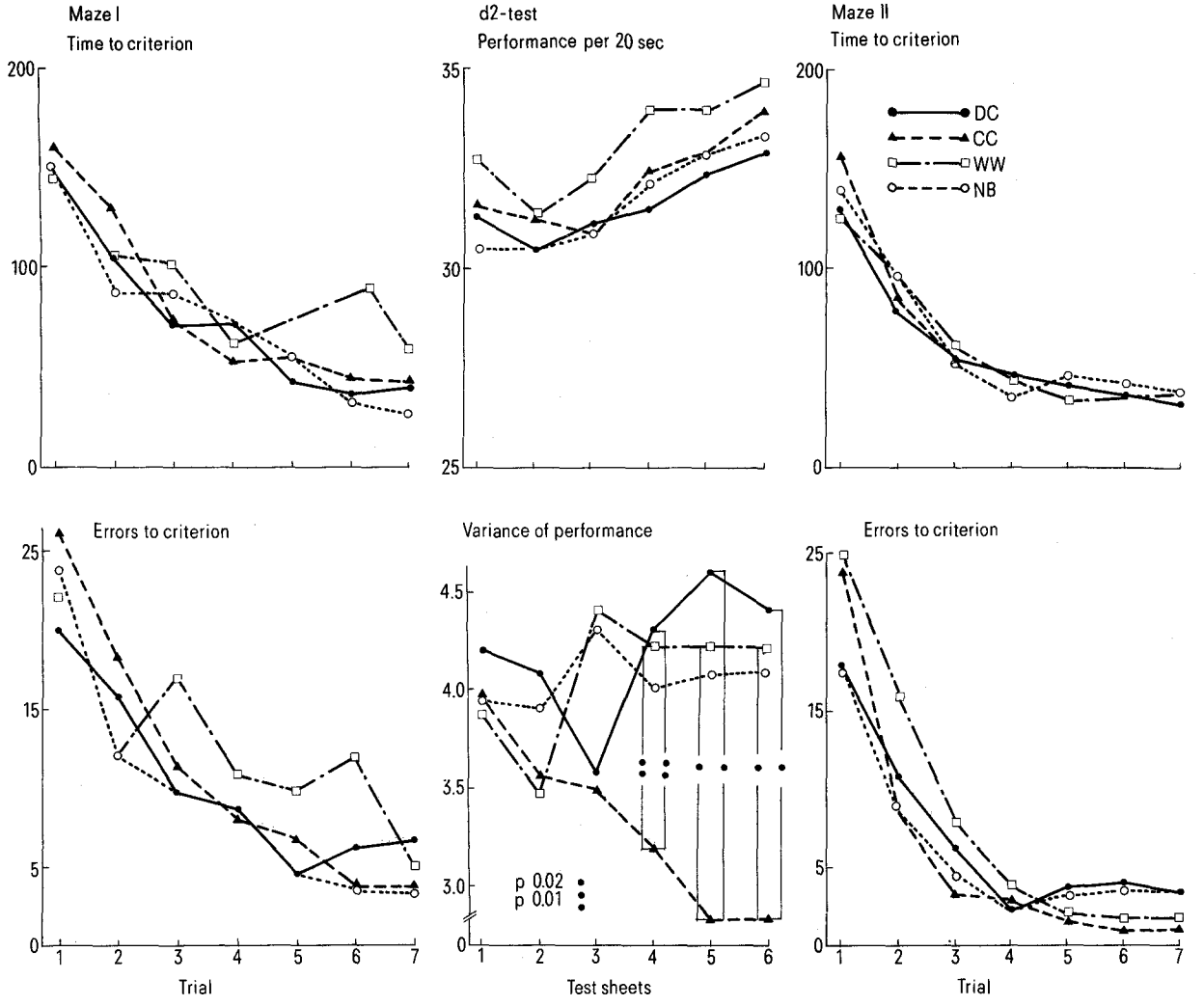

Figure 1. Mental maze learning and d2 letter cancellation task. Test averages were taken immediately after the first mental maze task.

decreases in the pulse amplitudes across the successive trials of Maze II were seen in 15 of the 16 subjects, reaching significance ($p \leq 0.05$ for regression coefficient b) in 11 subjects, whereas no consistent trends were seen in any of the other groups.

Although the development of EMG power, which also was not affected by the task program, suggests a post-application increase in muscle tension in the CC group, the respective intergroup t-values reached significance only against the NB but not against the two other control groups ($p < 0.05$ for the last d2 test period, $p < 0.001$ for the Maze II intertrial periods).

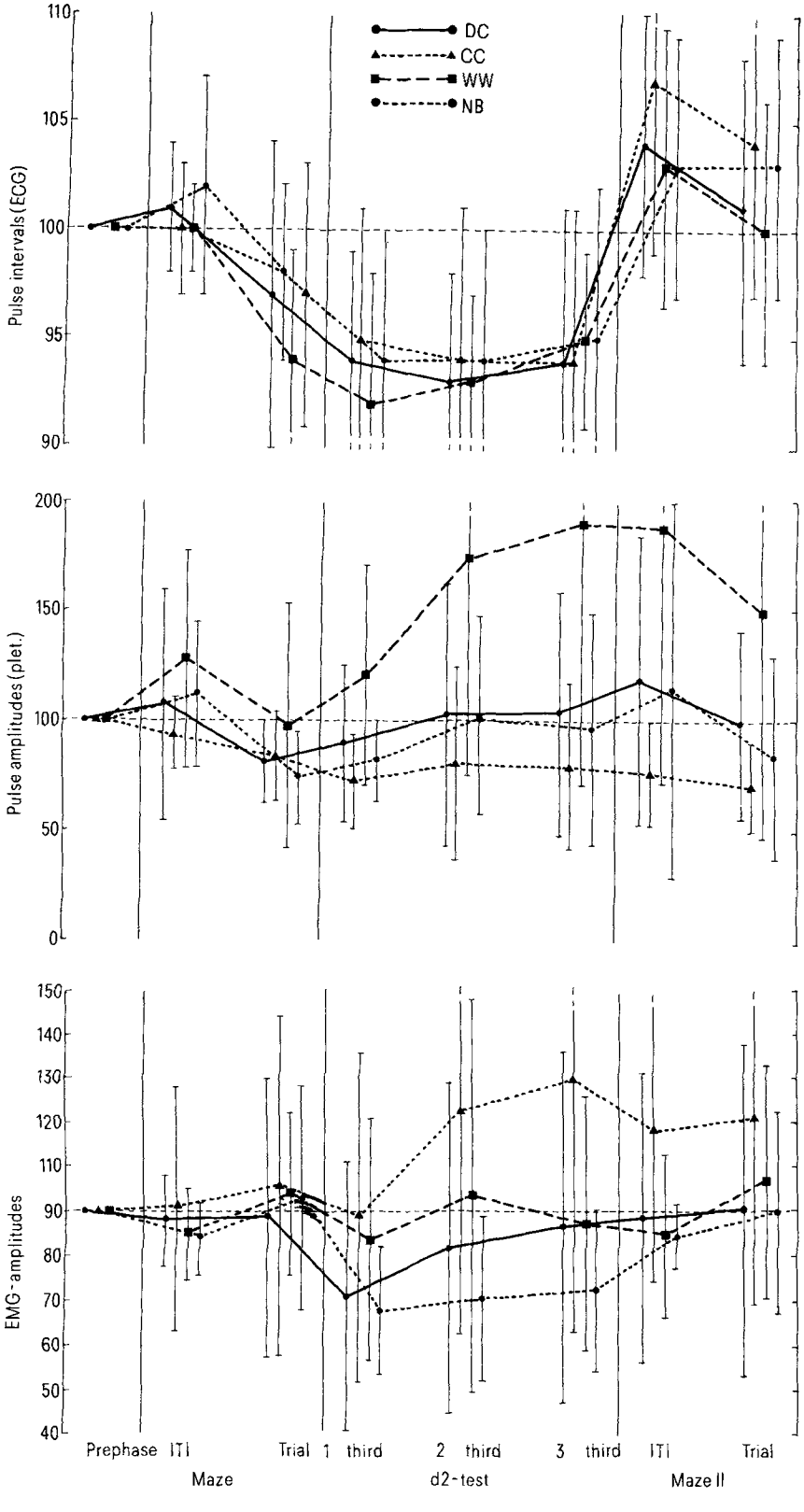

Figure 2. The development of heart rate, pulse amplitudes, and EMG across the successive testing phases, with administration of the experimental treatments immediately before the start of the d2 test.

No consistent effects were seen for respiration and skin conductance.

The conclusive crosscorrelational analysis across the entire data pool of the averaged physiological, the anamnestic, and the performance data revealed a significant positive correlation between self-reported caffeine and alcohol intake (Kendall +0.47, $r < 0.01$) within the rather low range of self-reported alcohol intake in this subject sample (1 to 6 occasions/week).

Discussion

The failure of caffeine to affect mental maze learning adds another element to the existing controversial literature which suggests that caffeinic effects on cognitive performance are highly task specific. With respect to the nature of the task specificity the present results are in line with an earlier observation by Lienert and Huber[22] and with a recent experiment by Broverman and Casagrande[5]. Lienert and Huber[22] found improvements in numerical, inductive, and spatial reasoning, tasks which required primarily intellectual speed, whereas other tasks requiring primarily intellectual power were not improved by caffeine. Broverman and Casagrande[5] found that caffeine impaired the detection of embedded figures when the task was novel and improved it when the task became routinized through previous practice.

In contrast, letter cancellation was positively affected by caffeine in that the regularity of performance, as determined by the intraindividual variance across successive 20-s periods, gradually increased so as to become significantly superior to the controls for the second part of the test. This result is particularly remarkable in view of the development of average performance. The number of correctly cancelled letters increased modestly but similarly in all groups across the testing period suggesting that the subjects performed this premium-rewarded task at their ceiling limits. The increase in regularity of performance in this experiment might therefore be considered as an indication of an increased easiness and fluency in processing repetitive information. Variance of performance has been considered only exceptionally in previous studies, as for instance in the already mentioned study by Lienert and Huber[22]. These authors remarked that while average performance remained the same, interpersonal variance was significantly reduced for those tests which were improved by caffeine.

The physiological effects accompanying this change in performance and the elevated saliva caffeine levels were generally modest. Heart rate was not affected in any appreciable way. This may be due to the fact that caffeine tends to affect heart rate in an antagonistic fashion by decreasing it through activation of the medullary vagal nuclei and by increasing it through a direct action on the myocardium[10,33]. Further, the outcome of this antagonism seems to vary with the dosage of caffeine, as small doses below 200 mg were more often reported to produce slight bradycardia and higher doses more often to produce tachycardia[33]. The dose of 300 mg, chosen in this experiment as a rough equivalent to the daily dose of an average coffee drinker or to the caffeine content of a double espresso[23], was therefore in a range where myocardial and vagal effects of the drug tend to balance each other. In contrast to the absence of an effect on heart rate, a consistent, although in its magnitude modest, acrodermal vasoconstriction significantly separated the caffeine treated group from the control groups throughout all postapplication periods of the experiment. In its magnitude this effect differed considerably from the greater changes usually seen in response to different emotional stimuli such as noise bursts[8] or conflict inducing Stroop stimuli[30] or in response to inhaling minute quantities of nicotine by smoking tobacco[1,30]. Therefore it seems reasonable to assume that the slight reduction in the acrodermal pulse amplitudes was a consequence of the dilating effect of caffeine on the general systemic blood vessels with the concomitant effect of a shift of blood volume into skeletal muscles, lungs, or coronary vessels, as reported by numerous clinical studies[16,27,29,33]. Taken together, the present findings suggest therefore that cardiovascular effects of a single acute dose of caffeine are surprisingly modest.

Muscle tension could be considered as another candidate for physiologic caffeinic effects in view of the fact that the drug stimulates muscle tonus in pharmacological preparations both directly and indirectly through nervous activation[16,33]. However, as such effects appear at higher dose levels only, it is of no surprise that significant effects have been reported only occasionally and only under particularly appropriate conditions, as by Asterita[3], who observed a decrease in the ability for muscular biofeedback relaxation after coffee ingestion. In parallel to such results the present experiment revealed a modest rise in muscle tonus after caffeine, which, however, reached significance in comparison to only one of the three control groups.

In summary, thus, it appears from the present experiment that a caffeine dose which increases the regularity and stability of routinized performance affects physiological parameters only to a modest extent. It suggests also that cognitive performance depending primarily on intellectual power is less susceptible to caffeinic action than cognitive performance depending on intellectual speed.

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A pivotal role for serotonin (5HT) in the regulation of beta adrenoceptors by antidepressants: reversibility of the action of parachlorophenylalanine by 5-hydroxytroptophan[1]

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Summary. An acute reduction in the synaptic availability of serotonin (5HT) by p-chlorophenlalanine (PCPA) nullifies the decrease in the density of cortical beta adrenoceptors caused by desipramine (DMI) but does not appreciably alter the attenuation of the norepinephrine (NE) sensitive adenylate cyclase. The analysis of competition-binding curves of [^{3}H]-dihydroalprenolol shows that the affinity of the agonist (–)-isoproterenol for cortical beta adrenoceptors is profoundly reduced following PCPA. This reduction in agonist affinity is enhanced by DMI. Resupplying 5HT by by-passing trptophan hydroxylase inhibition, by administering 5-hydroxytryptophan, converts a DMI non-responsive to a DMI responsive beta adrenoceptor population and shifts the markedly decreased agonist affinity towards the affinity values found in control preparations. The results demonstrate the pivotal role of 5HT in the regulation of the density and agonist affinity characteristics of cortical beta adrenoceptors and contribute to the scientific basis of the 'serotonin-norepinephrine link hypothesis' of affective disorders.
Key words. Cortical beta adrenoceptors; density; agonist affinity; role of serotonin; desipramine; p-chlorophenylalanine; 5-hydroxytryptophan.

Clinically effective antidepressant treatments – pharmacotherapy and ECT – cause, upon administration on a clinically relevant time basis, an attenuation of the norepinephrine (NE) sensitive adenylate cyclase in brain that is generally linked to a down-regulation of the density of beta adrenoceptors[22]. Experimental evidence