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Co-Dergocrine, Cerebral Glucose Utilization and Maze Performance in Middle-Aged Rats

RICHARD C. WALOVITCH,* DONALD K. INGRAM,† EDWARD L. SPANGLER† AND EDYTHE D. LONDON*[1]

**Neuropharmacology Laboratory, Addiction Research Center*
National Institute on Drug Abuse, Baltimore, MD 21224
and †Laboratory of Cellular and Molecular Biology, Gerontology Research Center
National Institute on Aging, Baltimore, MD 21224

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WALOVITCH, R. C., D. K. INGRAM, E. L. SPANGLER AND E. D. LONDON. *Co-dergocrine, cerebral glucose utilization and maze performance in middle-aged rats.* PHARMACOL BIOCHEM BEHAV **26**(1) 95–101, 1987.—The objective of this study was to determine the effect of co-dergocrine in rats on local cerebral glucose utilization and performance in a complex T-maze. Middle-aged (12–16 months) male Fischer-344 rats were given injections of co-dergocrine (3 or 10 mg/kg, IP) 35 min before behavioral testing or the administration of 2-deoxy-D-[l-^{14}C]glucose ([^{14}C]DG), a radiotracer for local cerebral glucose utilization (LCGU). Both doses stimulated LCGU in the locus ceruleus and median raphe nucleus and in subcortical structures associated with learning and memory (hippocampus and subiculum). The higher dose also stimulated LCGU in motor areas (caudate-putamen, globus pallidus, internal capsule). In contrast, co-dergocrine decreased LCGU in the frontal cortex. Poorer performance in a complex maze (increased shocks, errors and run time) was observed in middle-aged as compared with younger animals (3 months). Acute co-dergocrine treatment did not improve performance of middle-aged rats in this task. Thus, in the present experimental paradigm employing single dose administration, co-dergocrine's stimulation of LCGU was not associated with an alteration of maze performance in age-matched animals.

Co-dergocrine Glucose utilization Learning and memory Maze performance Hydergine®

CO-DERGOCRINE mesylate (previously called dihydroergotoxine) is used to treat declines in mental capacity, particularly in the elderly [11]. Although the mechanisms which mediate co-dergocrine's potential behavioral effects have not been elucidated, results from biochemical *in vitro* studies indicate that the drug has multiple effects (see review in [25]), including influences on cerebral monoaminergic [16] and cholinergic systems [6]. Co-dergocrine interacts with brain receptors for dopamine and serotonin, and with α_1- and α_2-noradrenergic receptors. While it appears to be a non-competitive antagonist at α-noradrenergic receptors [25,26], it has mixed agonistic/antagonistic effects at central dopamine and serotonin receptors [9,25]. Effects on central monoamine metabolism are consistent with conclusions from receptor binding studies and indicate that co-dergocrine is a dopaminergic and serotonergic agonist and a noradrenergic antagonist [18].

In vivo studies with co-dergocrine support these neurochemical findings. Co-dergocrine reduces the frequency of ponto-geniculo-occipital waves in reserpine-treated cats, consistent with a serotonergic action [41]. Although co-dergocrine's effects on *in vivo* models of noradrenergic activity have not been studied, inhibition of central noradrenergic transmission may be a mechanism by which the drug provides benefit in the treatment of cerebral vascular insufficiency. Co-dergocrine and other α-adrenergic blockers have anti-ischemic effects in animal models of this condition [15,24].

Co-dergocrine's effects on *in vivo* models of dopaminergic activity have been investigated extensively. Although it has little effect, if any, on dopamine-mediated motor responses in rats [18], it produces a dopamine-mediated decrease in serum prolactin in rats and humans [2,28] and a dopamine-mediated emetic response in dogs [18]. A central dopaminergic activity has been postulated as the mechansim by which co-dergocrine blocks hypoxia-induced behavioral depression in rats [14].

Co-dergocrine also has effects on glycolytic enzyme ac-

[1]Requests for reprints should be addressed to Dr. Edythe London, at NIDA Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224.

TABLE 1
EFFECTS OF CO-DERGOCRINE ON PHYSIOLOGICAL PARAMETERS

	Minutes After [^{14}C]DG	Vehicle (n=7)	Co-Dergocrine 3 mg/kg (n=8)	Co-Dergocrine 10 mg/kg (n=7)
Heart Rate (bpm)	12	430 ± 20	371 ± 21	446 ± 23
	30	428 ± 16	395 ± 25	472 ± 33
Blood Pressure (systolic/ diastolic, mmHg)	12	128 ± 3 / 112 ± 4	82 ± 3* / 72 ± 3*	89 ± 4* / 77 ± 2*
	30	107 ± 6 / 96 ± 6	96 ± 4 / 82 ± 4	90 ± 5* / 76 ± 4
Rectal Temperature (°C)	12	34.9 ± 0.2	35.0 ± 0.3	34.3 ± 0.4
	30	35.1 ± 0.1	34.8 ± 0.2	34.7 ± 0.2

Each value is the mean ± SEM for the number of animals indicated in parentheses.
*Significant from control values ($p<0.05$) according to one-way ANOVA and Dunnett's test.

tivity [4]. When administered chronically to rats (1 mg/kg, IP for 25 days), it counteracted the age-associated decline (3–12 months) in hexokinase and increase in lactate dehydrogenase in the forebrain. However, acute treatment with the same dose of co-dergocrine had no effects on glycolytic enzyme activity. This difference may reflect an accumulation of co-dergocrine in the brain after chronic treatment [13].

In the present study, the effects of co-dergocrine on local cerebral glucose utilization (LCGU) and maze performance were tested in rats. Under normal conditions, glucose is the major substrate for oxidative metabolism of the adult brain [32,35]. A tight coupling between glucose metabolism and neuronal firing has been demonstrated in slices of rat cerebral cortex [23], and many other correlations between cerebral function and cerebral glucose consumption have been observed in intact animals [34]. Although co-dergocrine's effects on rates of cerebral glucose utilization have not been measured previously in intact animals, chronic co-dergocrine treatment counteracted the age-associated decline (at 12 vs. 2.5 months) in glycolytic enzyme activity in homogenates of rat forebrain [4], suggesting an increased capacity for cerebral glucose utilization.

Because it was of interest to determine if co-dergocrine could enhance cerebral glucose utilization *in vivo*, we measured LCGU in middle-aged rats by the 2-deoxy-D-[1-^{14}C]-glucose ([^{14}C]DG) procedure. Using this technique, decrements in LCGU have been observed previously in rats by midlife [19]. To determine if the co-dergocrine treatment used in this study facilitated performance in a learning paradigm, we also tested a separate group of rats in a 14-unit T-maze. The 14-unit T-maze is a reliable test of complex problem solving and has yielded robust evidence of age-related performance impairments in rats and mice [12]. A preliminary report on the effects of co-dergocrine on LCGU has been published in a review [20].

METHOD

Subjects

Male Fischer-344 rats were obtained from the Charles River Breeding Laboratories (Wilmington, MA) or Harlan Sprague Dawley Inc. (Indianapolis, IN). Two age groups were selected: young (3 months) and middle-aged (12–16 months). Behavioral studies were performed using rats of both ages. However, LCGU was determined only in the middle-aged animals because LCGU reportedly declines by midlife with no further decrement during senescence of the Fischer-344 rat [19]. The rats were housed doubly in suspended metal cages, and were provided water and food (NIH-07 formula) ad lib, except where noted. The vivarium was maintained at 22±1°C on a 12-hr light:12-hr dark photocycle (lights on at 0800 hr).

Drug Treatment

Co-dergocrine (Hydergine®, Sandoz, 3 or 10 mg/kg) was injected intraperitoneally 35 min before behavioral testing or the injection of [^{14}C]DG. Corresponding control rats were injected with an equal volume of the vehicle (propylene glycol, 1 ml/kg body weight). The drug was mixed fresh daily.

Preparation for LCGU Experiments

All animals were food-deprived for approximately 19 hr before surgery. Anesthesia was induced by placing the animal in a small Plexiglas® chamber that was flooded with 5% halothane (Ayerst Laboratories, South Plainfield, NJ) at a flow rate of 2–3 liters/min of 100% O_2. The animal was removed from the chamber and placed on a heating pad. Anesthesia was maintained for 15–30 min, with 1–2% halothane at a flow rate of 2–3 liters/min of 100% O_2.

Halothane-anesthetized rats were prepared with indwelling catheters in the left femoral vein and artery. The animals then were partially immobilized and placed in a sound-insulated wooden chamber [19], where they were allowed to recover from surgery for at least 3 hr prior to [^{14}C]DG administration. During this time period, their body temperature was monitored with a rectal thermoprobe connected to a feedback device that heated the chamber when body temperature fell below 35°C.

Determination of LCGU

[^{14}C]DG (125 μCi/kg body weight) was administered intravenously, and timed arterial blood samples were collected and centrifuged. Aliquots of plasma were taken for assessment of glucose and [^{14}C]DG concentrations using a Beckman Glucose Analyzer II (Beckman Instruments, Irvine, CA) and liquid scintillation spectrometer (Beckman), respectively. Rats were killed 45 min after the [^{14}C]DG injection by an intravenous overdose of sodium pentobarbital (60 mg in 1 ml, Abbott Laboratories, North Chicago, IL). Brains were removed immediately and frozen in 2-methylbutane (Fischer Scientific Co., Silver Spring, MD) at −60°C.

Frozen 20 μm brain sections were cut in a cryostat, dried quickly, and apposed to Kodak SB-5 X-ray film along with [^{14}C]methyl methacrylate standards for 6–8 days. Radioactivity was determined by quantitative autoradiography using a Leitz Orthoplan microscope with a microdensitometer (model 560/DADS; E. Leitz, Inc., Rockleigh, NJ). The autoradiograms from three to six sections of tissue were used for each brain area measurement. Six measurements of optical density were taken from each hemisphere for bilateral brain areas; six measurements also were taken from midline structures. All measurements were taken using a square reticule, which was 0.09 mm long on each side.

LCGU was calculated from brain and plasma radioactivities and plasma glucose concentrations, as previously described [33].

Physiological Assessments

Effects of drug treatments on the following parameters during the [^{14}C]DG experiments were evaluated: pulse rate, arterial systolic and diastolic blood pressure, and body temperature. Blood pressure and pulse rate were recorded by connecting the arterial catheter to a strain gauge transducer (Statham Instruments Co., Hatorey, PR), coupled to a paper chart recorder (Gould Recorder 2200, Gould Inc., Cleveland, OH).

Behavioral Testing Apparatus

Pretraining for one-way active shock avoidance was conducted in a straight runway, which has been described in detail previously [36]. Training also involved shock avoidance and was conducted in an automated, 14-unit T-maze. The configuration, dimensions, and construction of this maze have been described [10, 12, 36]. Performance parameters, including errors (deviations from the correct path, run time from start area to goal box, number of shocks, and duration of shock), were scored for each trial.

Maze Training Procedure

All training was conducted during a one-day session beginning about 0900 hr and ending about 1600 hr. The rats that were run during a session were brought to the room containing the mazes and were kept in plastic cages for at least 30 min prior to training.

Pretraining involved one-way active avoidance in a straight runway, using procedures described previously [36]. The rats continued to receive pretraining trials until a criterion of eight out of ten successful avoidances was achieved. When this criterion was met, the animals were returned to the holding cages for intervals ranging from 1–3 hr before

TABLE 2

EFFECTS OF CO-DERGOCRINE ON LOCAL CEREBRAL GLUCOSE UTILIZATION

Brain Region	Vehicle (n=7)	Co-Dergocrine 3 mg/kg (n=8)	Co-Dergocrine 10 mg/kg (n=7)
Motor Areas			
Pyramidal Fibers	23 ± 2	27 ± 3	27 ± 1
Internal Capsule	22 ± 2	28 ± 2	31 ± 3*
Caudate-Putamen	63 ± 3	76 ± 4	80 ± 3*
Globus Pallidus	46 ± 3	50 ± 3	60 ± 3*
Red N.	58 ± 4	59 ± 3	66 ± 4
Substantia Nigra Pars Compacta	51 ± 4	61 ± 3	63 ± 4
Substantia Nigra Pars Reticulata	39 ± 2	47 ± 2	57 ± 4*
Zona Incerta	72 ± 6	76 ± 5	81 ± 1
Ventrolateral N., Thalamus	73 ± 4	79 ± 4	89 ± 3*
Cerebral Cortex			
Pyriform	51 ± 5	59 ± 3	61 ± 4
Retrosplenial Medial	76 ± 5	76 ± 2	79 ± 4
Precentral Medial	80 ± 6	83 ± 3	87 ± 4
Sensorimotor (Layer IV)	80 ± 5	79 ± 1	84 ± 1
Frontal (Layer IV)	88 ± 2	71 ± 2*	78 ± 2*
Frontal (Layer V)	75 ± 3	65 ± 1*	74 ± 3
Auditory (Layer IV)	92 ± 5	95 ± 2	102 ± 5
Entorhinal Cortex	59 ± 4	59 ± 4	66 ± 2
Learning and Memory			
Dorsal Hippocampus			
CA1	42 ± 3	44 ± 2	51 ± 4
CA2–CA3	48 ± 4	55 ± 2	57 ± 4
Dentate Gyrus	47 ± 4	49 ± 2	60 ± 5
Ventral Hippocampus			
CA1	50 ± 4	57 ± 3	62 ± 4
CA2–CA3	53 ± 4	57 ± 3	64 ± 4
Dentate-Gyrus	50 ± 4	55 ± 2	59 ± 3
Parasubiculum	64 ± 4	78 ± 4*	78 ± 2*
Presubiculum	67 ± 4	76 ± 4	79 ± 2*
Subiculum	63 ± 3	69 ± 3	73 ± 1*
Anterodorsal N., Thalamus	70 ± 4	77 ± 5	92 ± 6*
Anteroventral N., Thalamus	75 ± 4	77 ± 5	93 ± 5*
Medial Mamillary N.	83 ± 5	94 ± 3	102 ± 5*
Medial Septum	59 ± 3	64 ± 4	71 ± 3
Amygdala	48 ± 4	57 ± 2	61 ± 4*
Medial Forebrain Bundle	47 ± 6	59 ± 3	66 ± 4*
Autonomic Function			
Paraventricular N.	68 ± 5	80 ± 3	81 ± 7
Medial Preoptic Area	47 ± 5	51 ± 5	63 ± 3*
Posterior Hypothalamic N.	56 ± 4	66 ± 6	80 ± 5*
N. Tractus Solitarius	60 ± 3	71 ± 4	74 ± 7
N. Reticularis Lateralis	38 ± 3	46 ± 5	48 ± 3
Locus Ceruleus	56 ± 4	70 ± 3*	77 ± 4*
Medial Raphe N.	65 ± 7	86 ± 4*	82 ± 2*
Dorsal Raphe N.	63 ± 3	74 ± 3*	73 ± 3

Each value (μmol/100 g/min) is the mean ± SEM for the number of animals indicated in parentheses.

*Significant from control ($p \leq 0.05$) according to one-way ANOVA and Dunnett's test.

TABLE 3
MAZE PERFORMANCE AS A FUNCTION OF AGE AND TREATMENT

Variable	Age (Months)	Treatment	Trial Block (3 trials/block) 1	2	3	4	5	All
Errors/ trial	3	Vehicle	14.0 ± 1.1	5.2 ± 0.2	2.8 ± 0.2	1.1 ±0.2	1.1 ±0.5	4.8 ±0.5*
	12	Vehicle	23.0 ± 2.8	8.8 ± 1.8	4.0 ± 0.9	2.5 ±0.4	1.8 ±0.3	8.0 ±0.8
	12	Co-Dergocrine	24.8 ± 3.4	11.9 ± 3.0	6.4 ± 1.5	4.3 ±1.0	3.4 ±1.0	10.2 ±1.5
Run time (sec/trial)	3	Vehicle	95.1 ± 8.14	29.5 ± 5.4	21.7 ± 3.1	11.1 ±1.3	9.3 ±0.7	32.7 ±1.4*
	12	Vehicle	198 ±38.4	60.5 ±10.2	26.8 ± 6.1	17.9 ±3.3	18.7 ±3.7	64.5 ±9.1
	12	Co-Dergocrine	157 ±20.6	97.1 ±21.9	47.7 ±11.9	35.3 ±8.5	29.4 ±8.1	73.3 ±9.8
Shock duration (sec/trial)	3	Vehicle	66.0 ±10.0	5.7 ± 2.2	1.3 ± 0.7	0.1 ±0.1	0.0 ±0.0	14.6 ±2.0*
	12	Vehicle	151 ±34.3	30.1 ± 8.1	6.2 ± 2.7	1.6 ±0.6	0.9 ±0.4	37.9 ±6.2
	12	Co-Dergocrine	157 ±25.9	67.2 ±16.7	21.6 ± 8.2	6.1 ±3.7	4.2 ±1.9	51.1 ±8.0
Number of shocks/ trial	3	Vehicle	3.9 ± 0.3	1.7 ± 0.5	0.3 ± 0.2	0.1 ±0.1	0.0 ±0.0	1.3 ±0.1*
	12	Vehicle	4.7 ± 0.1	3.3 ± 0.5	1.7 ± 0.4	0.9 ±0.4	0.6 ±0.3	2.2 ±0.3
	12	Co-Dergocrine	4.9 ± 0.17	4.0 ± 0.4	2.9 ± 0.6	1.1 ±0.4	1.2 ±0.5	2.8 ±0.4

Each value is the mean ± SEM for 7 animals. Co-dergocrine (3 mg/kg IP) or vehicle (propylene glycol) was injected 35 min before behavioral testing.
*Young group was significantly different from both middle-aged groups, according to Dunnett's test ($p \leq 0.05$).

beginning maze training. Only animals meeting the pretraining criterion were used for maze training.

For the first trial of maze training, each rat was placed in the start area of the 14-unit T-maze for 5 sec. Then a guillotine door was raised to permit access to the maze. The animal was allowed 10 sec to move through approximately one-fifth of the maze, which corresponded to the distance in the straight runway. There was no punishment for incorrect responses (i.e., entries into arms deviating from the true path). Successful negotiation through each segment of the maze was followed by the lowering of a guillotine door to that segment to prevent backtracking. The animal could receive a maximum of five shock episodes during one trial. The maximum shock exposure per trial was 300 sec, at which time the animal was removed from the maze. If an animal was so removed for three trials during training, it was eliminated from the experiment. The trial ended when the rat entered the black goal box. Each animal received a total of 15 trials with a 2-min intertrial interval. Between trials, the maze was raised by a motorized pulley system so that the grid floor could be wiped with a 90% ethanol solution to mask possible odor cues.

Statistical Analyses

Statistical significance of drug effects on LCGU and physiological parameters was determined by one-way analysis of variance, with multiple comparisions performed using Dunnett's test. Data on errors, response times, number of shocks received, and duration of shock exposure as a function of training blocks (3 trials per block) were analyzed in separate 3 (group) by 5 (training block) analyses of variance (ANOVA) with repeated measures on the last factor [39]. The criterion for statistical significance was taken as $p<0.05$.

RESULTS

Physiological Parameters (Table 1)

Co-dergocrine treatment did not alter heart rate or rectal temperature during the [^{14}C]DG procedure. The lack of effect on rectal temperature may reflect the fact that the animals were heated externally during the experimental procedure. In contrast, both doses of co-dergocrine decreased systolic and diastolic blood pressure. The effect on systolic blood pressure after the high dose was still apparent 1 hr after drug administration.

LCGU Effects (Table 2)

In general, co-dergocrine produced a dose-dependent increase in LCGU in subcortical structures. However, this effect reached statistical significance in most brain regions only at the high dose (10 mg/kg). This dose produced increases of 22–46% over mean control values in many brain areas associated with motor function, such as the caudate-putamen, globus pallidus, substantia nigra pars reticulata, and the ventrolateral thalamus.

Enhanced LCGU also was observed in brain areas asso-

ciated with learning, memory and motivation. Whereas the parasubiculum showed increased LCGU in response to 3 mg/kg co-dergocrine, the higher dose also increased LCGU in other limbic areas, such as the presubiculum, subiculum, amygdala and components of the Papez circuit (anterior thalamus, medial mammillary nucleus). The LCGU in the medial forebrain bundle was increased by 40% over control values after 10 mg/kg co-dergocrine. In contrast, no significant LCGU stimulation was observed in the cerebral cortex. In fact, a significant decrease was observed in the frontal cortex.

Brain stem nuclei containing monoaminergic cell bodies, such as the medial raphe nucleus and locus ceruleus, showed an increase in LCGU after treatment with either dose of co-dergocrine. The medial preoptic area and the posterior hypothalamic nucleus, which are related to thermoregulation, also showed increased LCGU after 10 mg/kg co-dergocrine.

Behavioral Results (Table 3)

All of the 32 rats completed pretraining, but only 20 rats completed the 15 trials of maze training. Data on one animal each from the young and middle-aged control groups were lost due to mechanical failures. Data on shock number were lost for an additional animal in the middle-aged control group. Two animals in the middle-aged group receiving the low dose of co-dergocrine were excluded from the experiment because they consistently failed to avoid shock in the maze. This type of performance failure was most severe in the middle-aged experimental group receiving the 10 mg/kg dose. Only two of eight animals in this group completed maze training. In addition to "freezing" during shock exposure, rats injected with the high dose of co-dergocrine exhibited the following overt behaviors: ataxia, postural hypotension, lack of response to auditory and tactile stimuli. Because of the impairments attributed to the 10 mg/kg dose, maze performance data from this group were not analyzed.

All groups completing the 15 trials demonstrated learning in the maze task as evidenced by decline in all performance parameters as a function of trials (Table 3). The main effects of trial block, as revealed in the ANOVAs, were significant for all performance parameters (p's ≤ 0.0001). The main effect of group also was significant for all parameters (p's≤ 0.005). It was also evident from the Dunnett's analysis that the young group of control rats exhibited superior performance compared to the middle-aged groups on all parameters assessed (Table 3). The mean performance measures of the middle-aged control group appeared superior to that of the group receiving the acute 3 mg/kg co-dergocrine treatment; however, the drug effect was not statistically significant according to Dunnett's test ($p>0.05$).

Group by block interactions were revealed in the results of the ANOVAs of response times ($p<0.005$) and shock duration ($p<0.003$). Because of the significant group by blocks interaction, an analysis of the simple main effects of groups was conducted for each training block [39]. This analysis indicated that significant group differences in response times were confined to the first two training blocks. The young control group was significantly ($p<0.05$) faster than the middle-aged control and the co-dergocrine treated group during the first training block and faster than the co-dergocrine treated group during the second training block. Similarly, the young group had significantly less shock exposure than both the older groups during the first training block ($p<0.05$) and significantly less exposure ($p<0.05$) than the co-dergocrine group during the second training block.

DISCUSSION

The present results indicate that acute co-dergocrine treatment increases LCGU in many subcortical regions. However, this stimulation is not associated with a facilitation of performance in a shock-motivated 14-unit T-maze.

The interaction of co-dergocrine with central monoaminergic systems may explain some of the drug's effects on LCGU. Actions at presynaptic serotonin receptors may mediate the increase in LCGU observed in serotonin cell body areas, the median and dorsal raphe nuclei; whereas, the LCGU increases in the motor areas may partly reflect a dopaminergic agonistic activity.

The dopaminergic agonists, amphetamine and apomorphine, also increased LCGU in motor areas of the rat brain [21]. Apomorphine produced locomotor activation (reversal of reserpine-induced akinesia, contraversive turning in rats with unilateral nigrostriatal lesions) and stereotypies at doses similar to those which stimulated LCGU. However, co-dergocrine stimulated LCGU at doses lower than those used previously to induce stereotypies and contralateral rotations [17,38]. Rats in the present study showed a locomotor impairment after treatment with 10 mg/kg co-dergocrine, which may have interfered with the animals' performance in the behavioral testing paradigm. The impairment was not at variance with former findings because stimulatory motor effects of co-dergocrine were seen previously after a latency of 1 hr, and an early depression of locomotor activity by co-dergocrine has been observed in mice [38]. It has been proposed that the early depression of locomotor activity in mice observed after treatment with ergot derivatives could be related to the stimulation of presynaptic dopaminergic autoreceptors [3,8].

Co-dergocrine's noradrenergic antagonistic action may have produced some of the LCGU effects observed. The decline in LCGU of the frontal cortex resembles the decrements observed after treatments with other α-adrenergic blocking agents (phentolamine, phenoxybenzamine, yohimbine) [29]. Like these other α-adrenergic antagonists, co-dergocrine increases LCGU in the locus ceruleus, medial forebrain bundle, and some nuclei associated with autonomic function [29,31]. Hemorrhagic hypotension also increases LCGU in the locus ceruleus and many autonomic nuclei (paraventricular, solitary, dorsal motor nucleus of the vagus) [30]. α-Adrenergic antagonist-induced hypotension may be related to the elevation in LCGU in brain areas associated with central blood pressure control [31]. In general, α-antagonists must decrease blood pressure by 40% or more before increases in LCGU are observed in autonomic nuclei [31]. The fact that co-dergocrine suppressed blood pressure by less than 40% may explain why LCGU was not affected in autonomic nuclei, except for the locus ceruleus, which showed a dose-dependent increase in LCGU.

The increase in LCGU of the locus ceruleus may reflect the direct interaction of co-dergocrine with α receptors. Increased firing of locus ceruleus cells occurs after administration of co-dergocrine and other α antagonists [27]. However, other pharmacological studies indicate that locus ceruleus inhibition of cortical cell firing is mediated by β-adrenergic receptors [1]. Thus, the co-dergocrine-induced decrease in cortical glucose utilization may reflect an α-receptor

mediated activation of locus ceruleus cells and a consequent facilitation of β-noradrenergic transmission.

The increase in glucose utilization in subicular areas of the hippocampal formation (Table 2) and terminal fields of their efferents, the anterior thalamic and medial mamillary nuclei [37], may reflect a co-dergocrine-induced increase in hippocampal neuronal activity. These structures have long been implicated as being important neuroanatomical substrates of learning and memory [5,21]. Chronic administration of a nootropic analog of adrenocorticotropic hormone to rats increased LCGU in the parasubiculum and anterior thalamic nucleus [21].

In contrast to co-dergocrine's effect on LCGU, the drug was ineffective in altering complex T-maze performance in the present study employing single dose administration. During behavioral testing, 10 mg/kg co-dergocrine, which increased LCGU, caused pronounced behavioral sedation (i.e., the animals showed little or no response to tactile or auditory stimuli; see above discussion of motor effects).

In another study, co-dergocrine was administered to rats before behavioral testing, and a facilitation of performance was observed [17]. Co-dergocrine (3 mg/kg, SC) was administered in that study on four consecutive days, 2–4 hr before a one-trial test in a Lashley maze. Similar to our findings, a sedative effect was seen on the first day of treatment. However, this effect subsided with repeated administration. The 4-hr co-dergocrine-treatment enhanced performance (i.e., decreased number of errors) as the number of trials progressed. The positive effects may have depended on the subchronic treatment regimen and the relatively long delay between treatment and testing. In another study, co-dergocrine enhanced post-training consolidation and retrieval without improving acquisition by mice in a T-maze footshock avoidance paradigm [7]. Thus, while co-dergocrine does not appear to enhance acquisition of an avoidance task (shock in a complex T-maze), it may enhance consolidation and retrieval in such tasks, and improve performance in appetitive tasks, such as the Lashley maze. Future studies applying co-dergocrine treatment in the current learning paradigm and other avoidance paradigms could focus on consolidation and retrieval.

It should be noted that the doses of co-dergocrine used in this study (3 and 10 mg/kg) were high in comparison with human doses (up to 4.5 mg/day) [40]. Also, while benefits from co-dergocrine usually result from long-term administration [40], the treatments were given acutely in the present study. It is possible that cerebral neurochemical effects, such as LCGU stimulation, may occur maximally at high doses; whereas, behavioral effects may be more evident at lower doses, especially since side effects such as sedation would be less likely to occur.

In conclusion, co-dergocrine produced selective dose-dependent increases in subcortical LCGU. Although single dose co-dergocrine stimulated LCGU in brain areas associated with learning and memory, this effect did not appear to be related to the acquisition of a complex maze task in which age-related performance impairments were observed.

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