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Reversal of Guanethidine- and Diethyldithiocarbamate-Induced Amnesia by Peripherally-Administered Catecholamines[1]

THOMAS J. WALSH[2] AND TIBOR PALFAI

Psychology Research Laboratory, Syracuse University, Syracuse, NY 13210

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WALSH, T. J. AND T. PALFAI. *Reversal of guanethidine- and diethyldithiocarbamate-induced amnesia by peripherally-administered catecholamines*. PHARMAC. BIOCHEM. BEHAV. **14**(5) 713–718, 1981.—The effect of peripherally-administered catecholamines on guanethidine- and diethyldithiocarbamate-induced amnesia of a PA training in mice was investigated. The amnesic effect of guanethidine could be blocked with 50 mg/kg DA, or 0.75 mg/kg NE when given either before, immediately, or 10 min after but not 90 min following PA. Epinephrine or a lower dose of DA could not attenuate the guanethidine-induced amnesia. The amnesic effect of diethyldithiocarbamate could be blocked with 50 mg/kg DA, 0.75 mg/kg NE or 0.5 mg/kg E when given either before, immediately or 10 min after but not 90 min following PA. The amnesic effects of these compounds were interpreted in terms of their peripheral antiadrenergic actions.

Amnesia Memory Antiadrenergic drugs Biogenic amines

A NUMBER of pharmacological studies have provided indirect evidence that the catecholamines, dopamine (DA) and norepinephrine (NE) participate in memory formation. For example, drugs which inhibit the synthesis of these transmitters, block their receptors or disrupt their intraneuronal storage have been reported to produce time- and dose-dependent retention deficits [5, 9, 17, 22, 23, 26, 31, 32, 34, 35]. In the past, investigators have commonly attributed the amnesic effects of these drugs to the disruption of a central catecholamine-mediated phase of information storage [1,10]. In light of recent evidence that peripheral adrenergic processes modulate memory formation, however, the necessity of invoking a central antiadrenergic action as a common mechanism of amnesia has been questioned [22,23]. In fact, recent evidence from our laboratory indicates that the peripheral catecholamine-depleting effects of a variety of drugs might be sufficient to account for their ability to impair retention. For example, reserpine's effects on learning and retention are apparently not correlated with its effects on brain catecholamines. A dose of 2.5 mg/kg reserpine given either 24 or 2 hours prior to passive avoidance conditioning produced comparable depletion of brain NE and DA at the time of training; however, the drug only produced amnesia if administered 2–5 hours before the training trail. Clearly, reserpine's amnesic gradient was not related to its time-dependent effects on brain NE and DA. In a subsequent study we reported that syrosingopine, a reserpine analogue with a predominantly peripheral action [36], also impaired retention of passive avoidance. The structural similarity and the correspondence between the time- and dose-effects of reserpine and syrosingopine on retention suggested a common mechanism of action for the amnesic effects of these drugs. Since syrosingopine impaired retention through the depletion of only peripheral catecholamines, we suggested that the peripheral antiadrenergic effects of these rauwolfia compounds was sufficient to account for their amnesic actions. Furthermore, we reported that systemically administered NE or DA could attenuate both reserpine- and syrosingopine-induced amnesia [24,36]. Since these amines do not cross the blood-brain barrier following peripheral administration, their amnesia-blocking effects might be mediated by peripheral adrenergic receptors. Taken together, the above observations suggest that reserpine and syrosingopine impair retention of a passive avoidance response by blocking a necessary sympathetic response to the training trial. If, in fact, peripheral catecholamines play a role in the retention of shock-motivated responding, then other antiadrenergic agents might also disrupt retention through their sympatholytic actions. Therefore, the present series of experiments investigated the role of peripheral catecholamines in the amnesic effects of guanethidine and diethyldithiocarbamate (DDC).

[1]We would like to thank Ciba-Geigy for supplying the guanethidine sulfate (Ismelin). Send reprint requests to Dr. Tibor Palfai, Psychology Research Laboratory, Syracuse University, 101 Stevens Place, Syracuse, NY 13210.

[2]Present address: U. S. Environmental Protection Agency, Neurotoxicology Division, MD-74B, Research Triangle Park, NC 27711.

EXPERIMENT 1

Guanethidine is an "adrenergic neuron-blocking drug" which produces a functional blockade of the sympathetic nervous system by preventing the release of NE from sympathetic nerve terminals [18, 19, 21]. Since guanethidine is a highly polar molecule it does not enter the nervous system and has no demonstrable effects on brain catecholamines following systemic administration [6,16]. A number of recent reports have focused on the behavioral effects of this drug in hopes of gaining a better understanding of the role played by peripheral catecholamines in learning and memory. It has been reported, for example, that guanethidine impairs retention of two-way active avoidance [14], passive avoidance [13,25] and water-motivated operant responding [29]. Taken together, these observations suggest that pharmacological blockade of peripheral NE release impairs retention performance. These data and other lines of evidence support the hypothesis that peripheral adrenergic mechanisms participate in modulating memory storage.

The purpose of the first experiment is to examine whether systemically-administered DA or NE or epinephrine (E) would counteract the guanethidine effect on memory. Since these catecholamines do not cross the blood-brain barrier [37] the antagonism they produce would further support a role for peripheral adrenergic processes in guanethidine-induced amnesia.

METHOD

Subjects

All experiments were performed on male white Swiss mice bred in the Psychology Research Laboratory at Syracuse University from parent stock of the CD-1 strain obtained from Charles River Breeders, Wilmington, MA. The mice were housed in standard Econo plastic cages, typically four per cage, in a temperature (21°C) and humidity (50%) controlled environment. Purina laboratory chow and tap water were continuously available and a 12-hour light-dark cycle was in effect (8:00 a.m.–8:00 p.m. on). At the time of testing all animals were 60–90 days of age and weighed between 30 and 50 grams.

Apparatus

A step-through passive avoidance apparatus similar to the one introduced by Jarvik and Kopp [15] was used. The apparatus consisted of a V-shaped trough which was divided by a narrow guillotine door into a small illuminated start box and a larger darkened section. Stainless steel panels formed the walls and floor of the trough and served, in the darkened section, to deliver an AC electric shock from a Grason-Stadler Model 700 Constant Current Shock Generator to the animals' feet.

Procedure

Passive avoidance training consisted of placing the mouse into the illuminated start chamber; 60 sec later the guillotine door was opened and the latency to step-through into the darkened section was electronically timed. Immediately following step-through (defined as the passage of the hind limbs beyond the threshold), the door was closed and the mouse given a 1 mA footshock for 3 sec. All retention tests were given 7 days following the initial training session to allow for recovery from possible nonspecific drug effects. The mouse was again placed into the start box and 60 sec later the door was opened and step-through latency recorded to an arbitrary maximum of 300 sec. The step-through latency served as the dependent measure and was taken to indicate the degree of retention of the task.

Training and testing were performed between 10:00 a.m. and 3:00 p.m. so as to minimize the potential influence of endogenous behavioral and/or biological circadian rhythms on retention.

Pharmacological Procedure

Since guanethidine has been reported to impair retention when administered either before or after passive avoidance training [8,25], we examined the effects of catecholamines on guanethidine-induced amnesia following two amnesic doses and treatment-training intervals. All animals received one of two amnesic doses of guanethidine sulfate (Ismelin, Ciba). These doses (calculated as the salt) were 10 mg/kg administered immediately after training or 40 mg/kg injected 2 hrs before training. These groups also received a second injection of either 10 or 50 mg/kg DA, 0.5 or 0.75 mg/kg NE or 0.1 or 0.5 mg/kg E 15 min before passive avoidance training. These catecholamine dosages and time interval were chosen on the basis of their proven effectiveness in blocking reserpine- and syrosingopine-induced amnesia [24,36].

Results and Discussion

A Kruskal-Wallis nonparametric analysis of variance indicated a significant effect of catecholamines on guanethidine-induced retention deficits ($H(6)=12.85$, $p<0.05$; $H(6)=15.37$, $p<0.02$) for 10 mg/kg 0 post- and 40 mg/kg 2 hr pre-PA, respectively. Group median step-through latencies along with the results of post hoc Mann-Whitney U tests are presented in Table 1. As presented in the table, both 50 mg/kg DA and 0.75 mg/kg NE, but not lower doses of these catecholamines, prevented the guanethidine-induced amnesia. The step-through latencies of these groups were statistically different from the guanethidine+vehicle (distilled water) injected controls. The group-administered 0.5 mg/kg E had a median step-through latency of 210 sec during the retention test. The importance of this finding is obscured by the fact that 48% of the animals in this group died. Due to the lethal nature of this drug interaction, it is not possible to derive any conclusions concerning the role of E in the amnesic effects of guanethidine.

The results of this experiment demonstrate that the retention impairments produced by the pre- or post-trial administration of guanethidine can be reversed by appropriate doses of peripherally-administered DA and NE. The next experiment examined the time-dependence of the antagonism produced by systemically-administered catecholamines on guanethidine-induced amnesia.

EXPERIMENT 2

To restrict the effects of peripherally-administered catecholamines to memory consolidation processes, as opposed to their potential effects on acquisition, groups of mice were administered amnesic doses of guanethidine (40 mg/kg 2 hr before *or* 10 mg/kg immediately after PA training) which were followed by injections of either 50 mg/kg DA, 0.75 mg/kg NE or 0.5 mg/kg E at one of three post-training intervals. These intervals were immediately, 10 or 90 min following passive avoidance training.

TABLE 1

EFFECTS OF DA, NE AND E ON GUANETHIDINE-INDUCED AMNESIA*

Guanethidine Treatment	n†	Mortality (%)	IQ	Median
10 mg/kg, 0 post-PA				
G + 10 mg/kg DA	16	0	22–110	65
G + 50 mg/kg DA	13	0	164–300	265§
G + 0.5 mg/kg NE	12	0	79–235	106
G + 0.75 mg/kg NE	13	0	129–300	210‡
G + 0.1 mg/kg E	8	39	17–101	35
G + 0.5 mg/kg E	9	48	16–300	210‡
G + Vehicle	10	0	32–219	75
40 mg/kg, 2 hr pre-PA				
G + 10 mg/kg DA	14	0	13–154	64
G + 50 mg/kg DA	15	0	87–300	280§
G + 0.5 mg/kg NE	14	0	38–282	160
G + 0.75 mg/kg NE	15	0	91–300	200‡
G + 0.1 mg/kg E	9	31	7–25	20
G + 0.5 mg/kg E	10	33	20–59	37
G + Vehicle	10	0	20–119	45

*Mice were injected with either 10 mg/kg guanethidine immediately following PA or 40 mg/kg 2 hr prior to PA. The animals received a second injection of DA, NE or E 15 min before PA.

†Number of animals per group refers to only those mice that survived the drug administration.

‡$p<0.05$ vs G + vehicle.

§$p<0.01$ vs G + vehicle.

TABLE 2

TIME-DEPENDENT EFFECTS OF DA, NE AND E ON GUANETHIDINE-INDUCED AMNESIA*

Guanethidine Treatment	n†	Mortality (%)	IQ	Median
10 mg/kg, 0 post-PA				
G + DA 0	12	0	300–300	300§
G + DA 10	11	0	268–300	300§
G + DA 90	11	0	27–117	49
G + NE 0	11	0	196–300	300§
G +NE 10	12	0	123–300	300§
G + NE 90	11	0	52–252	79
G + E 0	6	45	13–132	91
G + E 10	8	28	8–100	23
G + E 90	8	33	8–300	126
G + Vehicle	10	0	49–183	62
40 mg/kg, 2 hr pre-PA				
G + DA 0	13	0	174–300	225‡
G + DA 10	13	0	180–300	255‡
G + DA 90	15	0	31–100	54
G + NE 0	12	0	39–300	288§
G + NE 10	12	0	56–300	282§
G + NE 90	13	0	31–85	56
G + E 0	7	30	21–63	44
G + E 10	6	54	10–105	32
G + E 90	8	28	25–101	37
G + Vehicle	8	0	12–143	70

*Mice were injected with either 10 mg/kg guanethidine immediately following PA or 40 mg/kg 2 hr prior to PA. The groups received a second injection of either DA (50 mg/kg), NE (0.75 mg/kg) or E (0.5 mg/kg) immediately, 10 or 90 min following PA.

†Number of animals per group refers to only those mice that survived the drug administration.

‡$p<0.05$ vs G + vehicle.

§$p<0.01$ vs G + vehicle.

Results and Discussion

The results of this experiment are presented in Table 2, along with the results of post hoc group by group statistical comparisons. As can be observed in the table, both DA and NE were able to block the guanethidine-induced amnesia when administered either immediately or 10 min following avoidance training. Animals administered NE or DA 90 min after training or E at any treatment-training interval did display the guanethidine-induced retention impairments. These data indicate that the memory impairments resulting from pharmacological inhibition of NE release from sympathetic nerve terminals can be prevented by systemically-administered NE or DA.

To summarize, the results of these experiments demonstrate that (1) pharmacological blockade of the sympathetic nervous system with guanethidine during or shortly following passive avoidance training impairs subsequent retention in a time- and dose-dependent manner and (2) administration of either NE or DA up to 10 min following training prevents the guanethidine-induced amnesia. Since these catecholamines are effective up to 10 min after the training trial, the effects of guanethidine on retention would appear to be due to an impairment of memory formation and not to the impaired acquisition of the task. Taken together, these results support the hypothesis that peripheral catecholamines modulate memory storage.

EXPERIMENT 3

Diethyldithiocarbamate (DDC) is a dopamine-β-hydroxylase inhibitor which produces a marked, yet transient, depletion of NE in the brain and periphery by blocking the enzymatic conversion of DA to NE [3]. Due to this relatively selective effect on catecholamine synthesis, DDC has been an important pharmacological tool in elucidating the involvement of NE in the neurobiology of behavior.

A number of reports examining the effects of DDC on memory formation have found that this agent produces retention impairments for a variety of tasks including passive avoidance, active avoidance and discriminated avoidance [12,25]. While it has been argued that DDC produces amnesia by depleting brain NE during a critical amine-dependent phase of memory consolidation, substantial evidence has been presented to the contrary. For example, Haycock and his colleagues [11] observed no correlation between the effects of DDC on brain NE and DA and subsequent retention performance. Moreover, Meligeni, Ledergerber and McGaugh [20] reported that DDC-induced retention impairments could be attenuated by subcutaneously-

TABLE 3

EFFECTS OF DA, NE AND E ON DDC-INDUCED AMNESIA*

Treatment	n	IQ	Median
DDC + 10 mg/kg DA	18	31–267	95
DDC + 50 mg/kg DA	18	77–300	180†
DDC + 0.5 mg/kg NE	16	19–121	43
DDC + 0.75 mg/kg NE	18	57–300	208†
DDC + 0.1 mg/kg E	11	27–103	59
DDC + 0.5 mg/kg E	11	89–300	231†
DDC + Vehicle	12	17–285	57

*Groups of mice were administered 900 mg/kg of DDC 2 hr prior to PA. All mice received a second injection of either DA, NE, E or vehicle 15 min before PA.

†$p<0.05$ vs DDC + vehicle.

TABLE 4

TIME-DEPENDENT EFFECTS OF DA, NE AND E ON DDC-INDUCED AMNESIA*

Treatment	n	IQ	Median
DDC + DA, 0 post	14	53–300	182†
DDC + DA, 10 post	15	32–300	220†
DDC + DA, 90 post	14	25–259	74
DDC + NE, 0 post	15	46–300	99
DDC + NE, 10 post	15	39–300	203†
DDC +NE, 90 post	14	35–164	70
DDC +E, 0 post	13	83–300	199†
DDC + E, 10 post	14	187–300	300‡
DDC + E, 90 post	13	21–106	49
DDC + Vehicle	10	17–108	44

*Groups of mice were administered 900 mg/kg DDC 2 hr prior to PA. All subjects received a second injection of DA (50 mg/kg), NE (0.75 mg/kg) or E (0.5 mg/kg) immediately, 10 or 90 min following PA.

†$p<0.05$ vs DDC + vehicle.

‡$p<0.01$ vs DDC + vehicle.

administered NE. These data indicate that DDC's effect on peripheral adrenergic processes might be sufficient to account for its amnesic effects. The next series of experiments elaborated upon the effects of systemically-administered catecholamines on DDC-induced amnesia.

Procedure

In this experiment independent groups of mice were administered 900 mg/kg DDC 2 hr prior to passive avoidance training. All groups received a second injection of either 10 or 50 mg/kg DA, 0.5 mg/kg NE or 0.10 or 0.50 mg/kg E 15 min before training. A control group was injected with DDC 2 hr before training and distilled water 15 min before training.

Results and Discussion

The Kruskal-Wallis analysis of variance indicated that the catecholamines did have a significant treatment effect ($H(6)=12.95$, $p<0.05$). The group median step-through latencies, along with the results of post hoc statistical comparisons are presented in Table 3. Administration of either 50 mg/kg DA, 0.75 mg/kg NE or 0.5 mg/kg E blocked the DDC-induced amnesia. These groups had step-through latencies that were significantly longer than the DDC+vehicle group. The injection of lower doses of these catecholamines had no effect on the retention impairments produced by DDC. These results indicate that the amnesic effects of DDC might be mediated by the peripheral antiadrenergic effects of this compound. The next experiment examined the time-dependent nature of the antagonism produced by DA, NE or E for DDC-induced amnesia. This experiment might help to clarify whether DDC impairs learning of the avoidance response or the consolidation of the required behavioral response.

EXPERIMENT 4

This experiment examined the time-dependent effects of DA, NE and E on DDC-induced amnesia. These catecholamines were injected following training so that their effects on memory consolidation processes could be more readily assessed.

Groups of mice were administered 900 mg/kg DDC 2 hr prior to avoidance training. All groups then received a second injection of either 50 mg/kg DA, 0.75 mg/kg NE or 0.5 mg/kg E at one of three post-training intervals. These intervals were immediately, 10 min or 90 min following avoidance training.

Results and Discussion

The Kruskal-Wallis analysis of variance indicated a significant treatment effect ($H(9)=18.54$, $p<0.05$). The results of this experiment, along with post hoc group by group statistical comparisons are presented in Table 4. As can be seen in the table, several of the catecholamine treatments proved effective in reversing the DDC-induced amnesia. For example, the step-through latencies of the groups administered either DA or E immediately after training *or* DA, NE or E 10 min after training were significantly longer than the latency of the DDC+vehicle group.

These data demonstrate that peripherally-administered catecholamines can prevent the disruptive effects of DDC on retention and thus replicate previous findings [20]. The time-dependent nature of the antagonism produced by catecholamine administration suggests that DDC impairs memory storage without appreciably affecting acquisition of the task. That is, mice under a fully amnesic dose of DDC during training and up to 10 min thereafter will exhibit good retention if catecholamines are injected up to 10 but not 90 min following the training trial. This could indicate that peripheral catecholamines exert a modulating influence on information storage that lasts for at least 10 min following an aversive conditioning trial.

The amnesia-blocking effects of DA and E are particularly interesting in light of the fact that DDC does not alter E levels and even slightly increases brain DA concentrations [8,10]. Therefore, the specificity of the pharmacological antagonism provided by systemic catecholamines for DDC-induced amnesia do not appear to be consistent with the mechanism of action of this drug. In fact, recent reports have demonstrated that a variety of treatments, including am-

phetamine, monoamine oxidase inhibitors, central or peripherally-administered NE, the alpha-adrenergic receptor blocker, phenoxybenzamine, and even the neuropeptide, vasopressin, are able to block the disruptive effects of DDC on memory storage and/or retrieval [2, 7, 27, 28]. The apparent lack of pharmacological specificity (i.e., adrenergic stimulants as well as blockers are equally effective) in modifying DDC-induced amnesia could indicate that NE depletion, while a correlate of DDC's effect on retention, is not the mechanism by which this drug produces amnesia [30].

GENERAL DISCUSSION

The results of the first two experiments demonstrate that guanethidine-induced amnesia can be blocked in a time-dependent manner by peripherally-administered catecholamines. Both DA (50 mg/kg) and NE (0.5 or 0.75 mg/kg) administered up to 10 min following passive avoidance training attenuated the guanethidine effect on memory. The effectiveness of these amines in blocking amnesia when administered post-training suggests that guanethidine, like reserpine and syrosingopine (see [24,36]), impairs memory consolidation processes without preventing the initial acquisition of the task. These data provide further support of the hypothesis that peripheral catecholamines somehow modulate the formation of long-term memory. Furthermore, guanethidine is reported to block the release of NE from sympathetic nerve terminals without altering the synthesis, release or turnover of E in the adrenal medulla [4,6]. Therefore, retention deficits are produced by guanethidine in the presence of a fully functional adrenal medullary system. This observation together with the reports of negligible effects of demedullation on acquisition and retention and the lack of an effect of E on reserpine-, syrosingopine- and guanethidine-induced amnesia suggests that peripheral *noradrenergic* processes and not E or sympathoadrenal activity, participate in the neurobiological storage of recent experiences.

The third and fourth experiments demonstrated that the retention impairments produced by the dopamine-β-hydroxylase inhibitor, DDC, could also be reversed by DA, NE or E administered up to 10 min after training. These data are consistent with a peripheral hypothesis of drug-induced amnesia; however, it is difficult to specify the mechanism by which DDC disrupts retention since a variety of pharmacological manipulations have been reported to inhibit the disruptive effects of this drug on memory. The apparent lack of pharmacological specificity in blocking DDC-induced amnesia together with the complex spectrum of pharmacological effects produced by this drug could indicate that DDC's effects on catecholamine metabolism do not mediate its amnesic action. In fact, Randt and his colleagues [30] suggest that alterations in neuronal activity of the midbrain reticular formation and the parietal cortex are a more important biological correlate of DDC-induced amnesia then depressed levels of NE in the central or peripheral nervous system. Clearly, due to the complex pharmacology of antiadrenergic drugs, it is difficult to specify the mechanisms through which drugs like DDC and reserpine produce amnesia.

In light of the experiments reported here several general conclusions seem appropriate. For example, the memory impairments produced by peripherally active antiadrenergic agents and the amnesia-blocking effects of systemically-administered DA and NE indicate that peripheral catecholamines exert an important modulating influence on memory storage processes. Furthermore, the results of these experiments indicate that peripheral aminergic mechanisms are involved in some early stage of memory formation. That is, pharmacological manipulation of peripheral catecholamines alters retention only if these treatments are presented in close proximity to the training trial. Taken together, these results suggest that peripheral catecholamine-dependent processes may be involved in a time-dependent manner in the formation of memory for an aversively motivated task.

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