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Pharmacological modulation of photically evoked afterdischarge patterns in hooded Long-Evans rats

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The pharmacological modulation of photically evoked afterdischarge (AD) patterns within a short-term habituation paradigm were examined in the hooded Long-Evans rat. Pharmacological arousal by amphetamine, pilocarpine, and physostigmine or induced thalamic suppression by trimethadione (Tridione) attenuated AD development. AD development was unaffected by saline, methyl atropine, and atropine. Pentylenetetrazol (Metrazol) was used as an AD potentiator and, as such, enhanced AD development following all drug conditions except within the physostigmine and methyl atropine sessions. It was determined that in the hooded rat AD varies only as a function of drug injected; time (habituation) was not a factor. The role of the reticulocortical projection system and the limbic system was incorporated in the explanation of the results. Significant differences were also noted between the pharmacology of AD parameters in hooded vs albino rats.

Iterative stimulation by single photic pulses evokes electrocortical bursts of rhythmic afterdischarges (ADs) in the primary visual cortex of the rat (Fleming, Rhodes, Wilson, & Shearer, 1972, 1973; Fleming, Wilson, & Shearer, 1973; Fleming Shearer, & Creel, 1974; Rhodes & Fleming, 1970; Shearer, Fleming, Bigler, & Wilson, 1974). In albino rats, this sinusoidal afteractivity is suppressed through pharmacological stimulation by adrenergic (amphetamine), cholinergic (pilocarpine, physostigmine), and thalamically active anticonvulsant drugs (Fleming et al, 1972, 1974; Shearer et al, 1974).

In correlated research, Fleming et al (1973) have demonstrated that AD total excursion (TE) patterns in hooded rats were at variance with those patterns evinced by albino rats. Two major differences were noted: (1) AD values for hooded rats were of a significantly lower magnitude than those recorded for albino rats, and (2) hooded rats did not display the characteristic initial increase and subsequent decrease in AD TE consistently observed as a function of time in the albino rat (Rhodes & Fleming, 1970). For the hooded rat strain, AD TE remained constant over time. These results were accounted for partially by potential differences in the receptive properties of the two visual systems. In terms of this interpretation, Creel, Dustman, and Beck (1970) have reported significant differences in visually evoked responses (VERs), which were related to anatomical differences in the visual systems of albino and hooded rat strains (cf. Lund, 1965).

Since there are between-strain differences in response to pharmacological arousal per se (Fuller, 1970; Meier, Hatfield, & Fushee, 1963), as well as the marked differences in VER and AD TE parameters between hooded and albino rat strains, the question arises whether AD TE in the hooded rat in response to pharmacological modulation is in the same direction and of the same magnitude as that already established in the albino rat (Fleming et al, 1972, 1974; Shearer et al, 1974). Thus, the intent of the present investigation was to determine systematically the effects of pharmacological arousal or induced thalamic abatement on AD TE in the hooded Long-Evans rat strain. The following report was a direct procedural replication of

the Fleming et al (1972, 1974) and the Shearer et al (1974) studies with the exception of the strain utilized.

METHOD

Ten hooded Long-Evans rats obtained from Blue Spruce Farms, Altamont, New York were used as Ss. Each rat was 90-120 days old at the start of the investigation. Surgical preparation for the experiment was carried out in the following manner: Each rat was anesthetized with pentobarbital sodium (50 mg/kg) and was surgically prepared with in-dwelling electrodes implanted over the right and left visual cortices at points 7 mm posterior to the bregma and 3 mm lateral to the midline. Electrodes were also placed in the bone over the cerebellum and frontal sinus for reference and grounding, respectively. At least 7 days of recovery were allowed before any treatment sessions were initiated. All experimental procedures were carried out with waking animals with mydriatic pupils (1% atropine sulfate). All animals were individually caged and maintained on ad lib food and water throughout all phases of experimentation.

A Grass Model PS2C photostimulator was used to deliver 10 μ sec light pulses to a reflecting hemicylinder. The hemicylinder was placed in front of a hammock in which an animal was held in light restraint. With the photostimulator lamp placed 70 cm behind and slightly above the hemicylinder, and with the stimulator intensity setting at 4 on a 1-16 scale, the illuminance of the reflecting surface was approximatley 5 fc.

Brain responses were amplified with Grass 7P5A preamplifiers and Model 7 polygraph driver amplifiers (bandwidth, 0.3 Hz-3 kHz; time constant 0.24 sec) and recorded on magnetic tape. VERs and ADs were summed with a Model 400B computer of average transients (CAT) over a 1-sec epoch. The VERs and associated ADs were plotted on 25 x 8 cm graph paper for parametric quantification.

Each rat was administered the following drugs D-amphetamine sulfate (2.5 mg/kg), physostigmine sulfate (0.4 mg/kg), trimethadione (Tridione, 100 mg/kg), pilocarpine hydrochloride (10 mg/kg), atropine sulfate (3.0 mg/kg), atropine methyl nitrate (3.0 mg/kg), and 9% saline. The drugs were injected in equal volume amounts subcutaneously according to an individualized random schedule. A minimum of 4 days elapsed between drug treatments. The experiment was carried out in this manner: A rat was acclimated to the hammock for 15 min. Single photic pulses were then presented at a rate of 1/7 sec. Blocks of 25 consecutive responses each were summed by the CAT starting at 0, 5, and 15 min following the initiation of iterative stimulation. When the third block of responses had been recorded, the photic stimulation was interrupted, a drug injected, and a 15-min period elapsed before the iterative stimulation was resumed. Three blocks of 25 responses each were again recorded (0, 5, 15 min). When the third block of responses had been recorded, 10 mg/kg of Metrazol was immediately injected subcutaneously and, following approximately 7 min of continued photic stimulation, another block of 25 responses were recorded. The entire procedure required approximately 75 min to complete and yielded a series of three predrug and three postdrug plots and a plot indicating the AD response to the drug-Metrazol interaction.

VERs from the right visual cortex were plotted for each set of 25 photic pulses (cf. Fig. 1, Rhodes & Fleming, 1970). In order to gain an indication of TE changes for the AD activity, measures were taken by tracing the pen inscription of the AD of each plot from the third positive wave of the VER to the end of the 1-sec plot with a map-reading wheel. The data were analyzed with analysis of variance techniques.

RESULTS

Table 1 presents the results of analysis of variance tests in terms of TE values for the three postdrug and the one drug-Metrazol interaction measures. Newman-Keuls tests carried out on the basis of reliable analysis of variance scores (0 min, $F = 15.10$, $df = 6/54$, $p < .001$; 5 min, $F = 10.26$, $df = 6/54$, $p < .001$; 15 min, $F = 14.67$, $df = 6/54$, $p < .001$) indicate that during the 0-, 5-, and 15-min sampling periods, physostigmine, amphetamine, and pilocarpine, as contrasted to the control substances atropine, methyl atropine, and saline, significantly, although nondifferentially, depressed TE. Tridione significantly suppressed TE values only during the 15-min sampling period and reliably only when compared to saline. The use of atropine did not result in facilitation of AD TE.

The individual effects of Metrazol on each separate drug condition were ascertained by subtracting the TE of the 15-min sampling period from the subsequent Metrazol interaction values (see Table 1). Metrazol significantly potentiated TE for the saline, atropine, tridione, amphetamine, and pilocarpine drug conditions, while not affecting methyl atropine or physostigmine TE values. Newman-Keuls tests carried out on the basis of a reliable analysis of variance ($F = 6.02$, $df = 6/54$, $p < .001$) indicated that TE values for the

Table 1
Mean Total Excursion Values (± Standard Errors of the Mean) for Postdrug Sampling Periods

	Total Excursion (cm)					Row F Values df = 3/27
	0 Min	5 Min	15 Min	Metrazol	Metrazol – 15 Min	
Saline	66.4 ± 3.4	70.7 ± 6.0	78.7 ± 9.2	98.8 ± 10.2	20.1 ± 7.8*	9.73***
Methyl Atropine	62.8 ± 4.3	67.7 ± 4.5	74.5 ± 5.9	88.3 ± 10.6	13.8 ± 9.1	5.40***
Atropine	67.5 ± 5.2	76.9 ± 6.0	69.7 ± 5.2	79.6 ± 6.1	9.9 ± 3.9*	3.12*
Tridione	68.4 ± 4.0	68.1 ± 4.3	60.8 ± 5.0	77.9 ± 6.7	17.1 ± 6.7*	9.95***
Amphetamine	49.1 ± 2.9	54.3 ± 4.7	53.3 ± 2.9	73.4 ± 9.2	20.1 ± 6.2**	12.04***
Pilocarpine	49.2 ± 2.6	51.8 ± 3.0	53.5 ± 2.7	70.0 ± 5.3	16.5 ± 3.8**	17.74***
Physostigmine	47.8 ± 1.8	48.4 ± 1.5	50.4 ± 2.5	58.3 ± 5.2	7.9 ± 4.5	4.12*
Column F Values df = 6/54	15.10***	10.26***	14.67***	6.02***		

**Difference statistically significant at $p < .05$*
***Difference statistically significant at $p < .01$*
****Difference statistically significant at $p < .001$*

physostigmine-Metrazol condition were significantly lower than all other drug-Metrazol interactions, while amphetamine-Metrazol and pilocarpine-Metrazol conditions could only be differentiated from the saline-Metrazol condition.

Analysis of variance tests were also utilized to examine the effects of time on AD TE for each individual drug condition over the 0-, 5-, 15-min and drug-Metrazol sampling periods. Although analysis of variance scores indicate a significant difference over these sampling periods (see Table 1), Newman-Keuls tests revealed that this difference was attributed to the effects of the Metrazol sampling period. AD TE did not significantly vary across the 0-, 5-, 15-min sampling periods for any drug condition.

The possibility of sequential effects of the test conditions over time required treating the AD TE of the 5-min predrug sampling period with analysis of variance techniques. AD TE did not vary over the 5-min predrug conditions ($F = 1.58$, $df = 6/54$, $p < .10$). Thus, AD TE was not modified by the sequential effects of the experimental conditions per se.

DISCUSSION

Consistent with earlier reports on albino rats (Fleming et al, 1972, 1973; Shearer et al, 1974), the present investigation demonstrated that physostigmine, pilocarpine, amphetamine, and to a lesser extent Tridione, all significantly suppress AD TE in the hooded Long-Evans rat. Although the arousal drugs have different sites of pharmacological action, their effects on AD TE cannot be differentiated in the hooded rat. This observation is at variance with the data on albino rats which indicates that physostigmine can be differentiated from pilocarpine and amphetamine in terms of the most suppressive AD TE effect. Since a dose-response procedure was not utilized, the exact significance of this difference is problematical. Nonetheless, this difference does imply that the mode of action of these drugs on AD TE parameters may be different for the two strains. Thus, the data from the Fleming et al (1972) and the Shearer et al (1974) studies were utilized for direct comparison with the present data on the hooded rat. It should be noted that all procedures were identical for these three investigations. Difference and standard error of the difference scores (Edwards, 1972) revealed that saline, methyl atropine, and atropine control substances did not influence existing strain differences. For these drug conditions, albino Ss had significantly greater AD TE values than hooded Ss. However, this strain difference was abolished by amphetamine, tridione, pilocarpine, and physostigmine, although pilocarpine and physostigmine did exhibit a trend towards a difference of greater effectiveness in the albino strain. Furthermore, in albino rats AD TE varied as a function of time and drug. In the hooded rat AD TE varied only as a function of drug injected; time was not a variable.

The general explication of the effects of induced cholinergic and adrenergic arousal on AD TE may not only involve the pharmacological modulation of an ascending reticulocortical projection system (Krnjevic, 1974), as has been previously discussed (Fleming et al, 1972, 1974), but also the limbic system. Evidence is accumulating that the appearance of a theta pattern in the hippocampal limbic structure negates the development of photocally evoked ADs (Fleming & Bigler, in preparation; Pickenhain & Klingberg, 1967). It is not fully understood why hippocampal theta and AD are mutually exclusive; however, that a positive relationship exists between unit areas of the midbrain reticular formation and hippocampal synchronization (Klemm, 1970) denotes an important relationship between hippocampal theta and electrophysiological and/or behavioral arousal. Along this line of reasoning, cholinergic arousal by pilocarpine, physostigmine, and adrenergic arousal by amphetamine induces hippocampal theta (Bigler & Fleming, unpublished observations; Stumpf, 1965; Torri & Wikler, 1966) as well as attenuating AD TE. Dissimilarly, anticholindergics (e.g., atropine) decrease the development of hippocampal theta (Bigler & Fleming, unpublished observations, Torii & Wikler, 1966) and atropine like methyl atropine and saline have no effect upon AD TE. Thus, cholinergic and adrenergic stimulation of the upper and lower brainstem (Krnjevic, 1974), respectively, induces electrocortical and behavioral arousal which, as signaled by hippocampal theta, attenuates AD TE.

The results with Tridione are most likely related to its general depressive action upon the thalamus (Woodbury, 1969) and its putative specific depression of the lateral geniculate nucleus (see Shearer et al, 1974). Since the lateral geniculate nucleus of the thalamus is responsible for the cortical elaboration of VERs and ADs (Sumitomo & Klingberg, 1972), pharmacological depression of this area by Tridione attenuates AD TE.

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