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Differential Effects of Convulsants on Visually Evoked Responses in the Albino Rat

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BIGLER, E. D., D. E. SHEARER, R. E. DUSTMAN AND D. E. FLEMING. *Differential effects of convulsants on visually evoked responses in the albino rat.* PHARMAC. BIOCHEM. BEHAV. 8(6) 727–733, 1978. – Visually evoked responses (VERs) were recorded from primary visual cortex in unanesthetized albino rats during pharmacological modulation by one of the following convulsant agents: Physostigmine, picrotoxin, strychnine and Metrazol. The data were analyzed in terms of effects on VER components. The rat VER consists of six distinct waves constituted by three positive peaks (P1–P3) and three negative peaks (N1–N3). Results indicate a differential convulsant action on VER components. The administration of picrotoxin, resulted in a suppression of the peak amplitude of P1–N1 and delayed peak latencies of all components. Strychnine reliably shortened P1, N1 and P2 peak latencies, significantly increased N3 peak latency and only suppressed P3–N3 amplitude. Physostigmine essentially suppressed all component amplitudes but only increased peak latencies for P2 and P3 components. Metrazol, in general, was found to be relatively ineffective in the alteration of any VER component in a systematic manner. The data are discussed in terms of differential modes of convulsant action on the visual system. The results are likewise discussed with respect to their implications for convulsant modulation of photically evoked after-discharges.

Visually evoked responses Convulsants Physostigmine Picrotoxin Strychnine Metrazol

VISUALLY evoked responses (VERs) have been examined in a variety of seizure states and experimentally induced seizure conditions [4, 11, 13, 14, 19, 21, 26–29, 36]. Considerable attention has been directed by our laboratories [6, 17, 37] as well as others [23, 30, 40] in examining convulsant effects on VER after-discharge)AD), with VER AD and its modulation by convulsants and anticonvulsants likely providing an excellent model in experimental epilepsy [6, 30, 37]. Since convulsants can be differentiated by their actions on VER ADs, particularly with respect to their mode of convulsant action, we attempted to determine the following: (1) if similar differentiations could be established with convulsant drug action on the primary and secondary components of the visually evoked potential which precede AD, and (2) if convulsant drug effects on these components could provide a possible basis for the convulsant action on VER ADs.

METHOD

Animals

Ten male albino rats of the Holtzman strain, 90–120 days of age at the start of the investigation were anesthetized with pentobarbital sodium (50 mg/kg, IP) and surgically implanted with indwelling extradural stainless steel screw electrodes 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 calvarium and frontal sinus for reference and grounding, respectively. Seven days of postoperative recovery were allowed before the initiation of the drug treatment sessions. All experiments were carried out on waking animals with mydriatic pupils (1% atropine sulfate).

Apparatus

A Grass Model PS2C photostimulator was used to

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present 10 μsec light pulses to a refelcting hemicylinder. The hemicylinder was placed in front of a hammock in which an animal was held under light restraint. With the photostimulator lamp mounted 70 cm behind and slightly above the hemicylinder, the illumination of the reflecting surface was approximately 5 ft/c.

Brain responses were amplified with Grass 7P5A preamplifiers and Model 7 Polygraph amplifiers (bandwidth, 0.3 Hz–3 kHz; time constant, 0.24 sec) and recorded conventionally on magnetic tape. VERs were summated with a Model 400B Computer of Average Transients (CAT) over a 1 sec epoch and plotted on 25 x 38 cm graph paper by an X–Y plotter for parametric quantification.

Procedure

Each animal was administered the following drugs: Picrotoxin (2 mg/kg), strychnine (0.5 mg/kg), physostigmine (0.4 mg/kg), Metrazol, (10 mg/kg), and physiological saline. The drugs were injected in equal volume amounts subcutaneously according to an individualized random schedule. These dosages have been reported to reliably alter the VER AD [6,17] and were the standard dosage levels that have been used in previous pharmacological investigations of VER ADs [5, 6, 17, 18]. A minimum of four days elapsed between drug treatments. The experimental procedure was carried out in the following manner: A rat was habituated to the hammock for 15 min, then single photic pulses were presented at a rate of 1/7 sec. Following 5 min of iterative stimulation a block of 25 consecutive responses was summed by the CAT. Following recording, the photic stimulation was interrupted, a drug injected, and a 15 min period elapsed prior to the resumption of the iterative stimulation. Three additional blocks of 25 responses were recorded at 15, 20 and 30 min post drug injection. The entire procedure required approximately 60 min to complete and yielded a predrug and 3 post drug plots.

Measurement-Analysis

VERs for the right visual cortex were plotted for each set of 25 photic pulses. These responses typically included 3 positive-negative components labelled P1N1, P2N2, and P3N3 (see Fig. 1). The peak latency (in msec) was determined for each positive or negative component and the peak-to-peak amplitude (in μV) was measured for each component (e.g., P1N1, N1P2, P2N2, etc.).

RESULTS

The data are summarized in Tables 1 (for peak latencies) and 2 (for peak-to-peak amplitudes). The data were analyzed in two ways. First, across drug comparisons at each separate time interval were made with saline in each instance serving as a control. Secondly, each drug treatment was analyzed individually across time intervals. For these comparisons predrug levels served as controls. In both cases the data were subjected to analysis of variance techniques. Where significant F values occurred, the data were further analyzed via the Newman-Keuls mean-pairs comparison test, demonstrating the locus of significant differences.

Peak Latencies

P1 (20 msec). With across drug treatments, there were no significant effects by 15 min post injection. At 20 min post injection, both picrotoxin and Metrazol significantly increased peak latency when compared with strychnine, physostigmine and saline. By 30 min picrotoxin induced a significant increased latency that could be differentiated from all other drug treatments. In terms of pre- and post drug comparisons for individual treatments, a significantly shorter latency was found in all post saline and strychnine conditions while picrotoxin was associated with significantly increased delay times during the 20 and 30 min post drug conditions as compared to the predrug recordings. Also, Metrazol was associated with a significantly decreased latency time at 30 min as compared to 20 min.

N2 (27 msec). There was no significant across drug effects registered by 15 min post injection. Picrotoxin, by 20 min post injection, significantly increased N1 latency as compared to all other drug treatments. Similar effects were registered at the 30 min test point. No other across drug comparisons differed significantly. Picrotoxin reliably decreased post drug N1 latency as compared to predrug measures.

P2 (50 msec). There were multiple drug-by-time effects on P2 latencies. At 15 min following injection picrotoxin markedly increased P2 latency as opposed to all other drugs. This effect remained throughout the 20 and 30 min

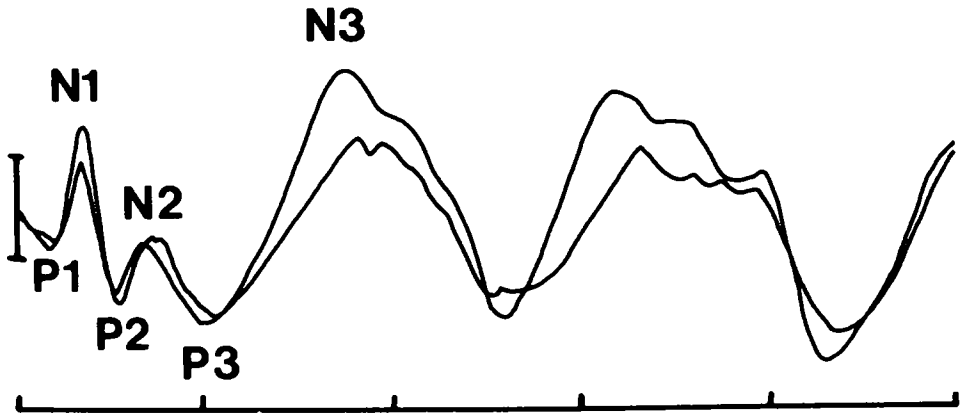

FIG. 1. Two typical superimposed EPs depicting the major positive-negative deflections. Calibrations: 50 μV, total time, 500 msec.

TABLE 1

MEAN PEAK LATENCIES IN MILLISECONDS (AND STANDARD DEVIATIONS) FOR VER COMPONENTS ACROSS DRUG AND TIME CONDITIONS†

Component		Saline Mean(SD)	Physostigmine Mean(SD)	Picrotoxin Mean(SD)	Strychnine Mean(SD)	Metrazol Mean(SD)	Significance
P1							
Predrug		19(3)	18(3)	18(3)	18(3)	19(3)	
Postdrug	15 Min	17(3)	17(3)	20(4)	17(3)	19(3)	
	20 Min	17(3)	17(6)	21(3)	17(2)	20(5)	**
	30 Min	17(2)	17(3)	21(3)	17(1)	18(2)	**
Significance		*		*	*	*	
N1							
Predrug		28(5)	28(6)	27(5)	28(5)	29(4)	
Postdrug	15 Min	27(4)	27(5)	29(5)	26(5)	29(5)	
	20 Min	27(4)	27(5)	34(7)	26(5)	29(5)	
	30 Min	27(4)	27(6)	32(6)	26(4)	29(6)	
Significance				*	*		
P2							
Predrug		50(4)	49(3)	48(4)	50(3)	52(4)	
Postdrug	15 Min	49(5)	51(3)	54(5)	47(4)	50(4)	**
	20 Min	49(3)	52(3)	56(5)	46(4)	51(4)	**
	30 Min	48(4)	52(2)	55(7)	47(3)	51(4)	**
Significance				*		*	
N2							
Predrug		80(5)	76(9)	78(6)	76(5)	76(8)	
Postdrug	15 Min	81(10)	77(9)	83(7)	75(5)	80(7)	**
	20 Min	78(6)	79(7)	85(9)	75(5)	79(6)	**
	30 Min	77(5)	78(9)	87(9)	74(5)	80(7)	**
Significance				*		*	
P3							
Predrug		97(11)	93(10)	95(8)	94(7)	92(12)	
Postdrug	15 Min	99(12)	98(8)	108(13)	102(11)	97(6)	**
	20 Min	99(10)	99(7)	11(10)	97(7)	97(7)	**
	30 Min	95(10)	100(9)	115(12)	99(8)	96(7)	**
Significance			*	*			
N3							
Predrug		162(11)	168(14)	163(11)	162(13)	163(14)	
Postdrug	15 Min	166(9)	171(19)	189(24)	174(11)	161(12)	**
	20 Min	170(11)	166(16)	187(18)	168(10)	161(12)	**
	30 Min	166(13)	168(20)	194(17)	166)10)	160(14)	**
Significance		*		*	*		

†Complete tables presenting actual F values and Newman-Keuls comparisons may be obtained by writing to the senior author.

*Significant (0.05) Column F score.

**Significant (0.05) Row F score.

test intervals. Strychnine had significant opposite effects, shortening P2 latency across all test intervals. Physostigmine by 30 min post injection significantly increased P2 latency as compared to saline and strychnine values. With respect to individual pre and post drug effects, physostigmine and picrotoxin increased P2 latency at 15, 20 and 30 min post drug intervals as compared to predrug measures while strychnine exhibited just the opposite effects by significantly shortening latencies at these post drug intervals. Metrazol and saline showed no reliable effects across pre- and post drug measures.

N2 (80 msec). At 15 min post injection of picrotoxin the N2 latency was increased and could be significantly differentiated from the strychnine decreased latency of N2. At 20 and 30 min this relationship remained in effect with the addition that picrotoxin significantly increased N2 latency as compared to strychnine, physostigmine, saline and Metrazol. Pre and post drug effects with individual drug comparisons showed only picrotoxin and Metrazol to have significant effects at all post drug sample intervals as compared to pre drug measures, for all other drugs there were no reliable pre- and post drug comparisons.

P3 (100 msec). Picrotoxin essentially increased P3 latency as compared to all other drugs for 15, 20 and 30 min. There were no other across drug significant comparisons. Physostigmine and picrotoxin exhibited sig-

TABLE 2

MEAN AMPLITUDES VALUES IN MICROVOLTS (AND STANDARD DEVIATIONS) FOR VER COMPONENTS ACROSS DRUG AND TIME CONDITIONS†

Component		Saline Mean(SD)	Physostigmine Mean(SD)	Picrotoxin Mean(SD)	Strychnine Mean(SD)	Metrazol Mean(SD)	Significance
P1N1							
Predrug		112(32)	118(26)	105(21)	97(22)	105(25)	
Postdrug	15 Min	108(28)	89(24)	81(36)	84(32)	86(23)	**
	20 Min	117(32)	95(21)	83(28)	93(35)	95(26)	**
	30 Min	107(29)	92(23)	95(30)	97(36)	92(33)	
Significance			*	*		*	
N1P2							
Predrug		152(59)	157(48)	150(48)	136(45)	144(54)	
Postdrug	15 Min	141(67)	104(41)	110(61)	124(70)	129(34)	**
	20 Min	150(53)	104(35)	105(51)	129(71)	137(51)	**
	30 Min	148(71)	107(35)	132(44)	131(70)	139(58)	
Significance			*	*			
P2N2							
Predrug		109(42)	107(25)	125(45)	110(32)	99(16)	
Postdrug	15 Min	104(32)	90(20)	108(44)	117(38)	115(33)	
	20 Min	113(42)	90(29)	97(41)	117(41)	121(28)	
	30 Min	124(52)	97(25)	114(35)	120(45)	124(27)	
Significance			*				
N2P3							
Predrug		41(19)	42(17)	33(15)	41(18)	30(15)	
Postdrug	15 Min	41(24)	51(27)	61(21)	53(24)	38(15)	
	20 Min	38(23)	46(23)	51(23)	48(16)	36(12)	
	30 Min	41(13)	41(24)	49(18)	45(15)	35(13)	
Significance							
P3-N3							
Predrug		133(56)	123(45)	101(31)	120(41)	110(37)	**
Postdrug	15 Min	107(35)	48(26)	102(49)	79(43)	100(33)	**
	20 Min	122(47)	37(26)	93(30)	85(42)	105(32)	**
	30 Min	108(42)	35(21)	96(45)	75(39)	95(25)	**
Significance		*	*		*		

†Complete tables presenting actual F values and Newman-Keuls comparisons may be obtained by writing to the senior author.

*Significant (0.05) Column F score.

**Significant (0.05) Row F score.

nificant effects in terms of individual pre and post drug comparisons. Both significantly increased peak latency for all post drug measures as compared to predrug measures. All other interactions with individual drugs were insignificant.

N3 (165 msec). Picrotoxin increased N3 latency as compared to all other drugs for all post drug sampling intervals. All other across-drug-by-time comparisons were nonsignificant. Relative to pre and post individual delay effects, picrotoxin significantly increased peak latency at all post drug levels as compared to predrug measures. Saline was associated with a significant difference in longer time delays when 15 and 20 min measures were compared to predrug levels. Strychnine could be differentiated from predrug measures at 15 min post drug.

Amplitudes

P1-N1 (110 μV). Physostigmine, Metrazol and picrotoxin reliably suppressed P1N1 amplitude at 15 min postdrug as compared to saline. At 20 min post injection, all the convulsants reliably suppressed component amplitude. There were no significant effects at 30 min post drug for any drug comparison. In terms of individual pre and post drug comparisons, physostigmine and picrotoxin reliably suppressed amplitude at all post drug intervals when compared to predrug measures. Metrazol suppression of amplitude was reliable only at the 15 min level when compared to predrug measures.

N1-P2 (150μV). Physostigmine at 15 min and physostigmine and picrotoxin at 20 min could be reliably differentiated from saline in terms of suppressive actions on N1P2 amplitude. With individual comparisons, physostigmine and picrotoxin were reliably associated with suppression of N1P2 amplitude. With individual comparisons, physostigmine and picrotoxin were reliably associated with suppression of N1P2 amplitude as compared to predrug measures at 15 and 20 min and physostigmine at 30 min.

P2N2 (110 μV). There were no significant differences

across drugs and sampling intervals. Physostigmine at 15 min post injection could be significantly differentiated in terms of amplitude suppression from predrug measures.

N2–P3 (40 μV). There were no significant differences across drug and injection intervals or with individual pre post drug comparisons.

P3–N3 (130 μV). Physostigmine reliably suppressed P3–N3 amplitude when compared to all other drugs and at all post injection intervals. Likewise, physostigmine's suppressive action on component amplitude could be significantly differentiated at all post drug levels from predrug measures. At 20 and 30 min post drug, strychnine reliably suppressed component amplitude as compared to saline, and similar suppressive actions were reliably registered at all post drug levels as compared to predrug measures. It should be noted that post saline 15 and 30 min measures were significantly lower than presaline measures.

DISCUSSION

To completely understand the modulation of the evoked potentials, the underlying mechanisms of the particular component in question must be known. Unfortunately, the neurogenesis of the various VER components in the visual system are not fully understood [2], but the following generalizations can be made: The initial primary components including at least P1 and N1 represent primarily retino-geniculate activity and the projection of such activity to visual cortex [12] as there is good correspondence between the driving of initial neuronal responses in lateral geniculate and the visual cortical representation of P1N1. At least N3 is a result, primarily, of lateral geniculate activity as there is a massive discharge of geniculate units that corresponds directly with the development of the N3 component [7]. These neurons in lateral geniculate presumably fire as a result of rebound excitation following the initial discharge with after-discharge activity occurring as a repetition of this event [7]. The origins of the intermediate secondary components, that is P2, N2, and P3, are the least understood but likely represent diffuse activity between the thalamus, midbrain and cortex (not restricted to that order) [12]. The following interpretations of the effects of various convulsants on VERs will be made with this framework in mind.

Picrotoxin

In general, picrotoxin suppressed the amplitude of only the first two initial components yet reliably delayed peak latencies of all components. The explanation of amplitude suppression and delay of peak latencies of the initial primary components requires consideration of at least two points: (1) Gamma-aminobutyric acid (GABA) has been implicated as an inhibitory mechanism in the vertebrate retina [10, 16, 22] and picrotoxin is thought to be a GABA antagonist [35,39], although there is much speculation and debate as to the exact specificity of picrotoxin action on GABA [35]. Intravitreally injected picrotoxin, depending on the dose, suppresses electroretinograms and increases the latency of tectal evoked responses in chickens [10]. Likewise, depending on the dose given, picrotoxin may depress the activity of isolated cat optic nerve fibers [20]. Thus, the suppression of P1N1 amplitude, since a large part of the P1N1 complex is retinal dependent, may be a result of systemically administered picrotoxin causing the alteration of retinal inhibitory mechanisms which, in turn disrupt visual system neural transmission from retina to geniculate. Since it is conceivable that the initial components may be affected in such a manner it is plausible to assume that increased latencies in subsequent components is a function of this increased delay. (2) As indicated previously picrotoxin is a GABA antagonist and GABA has been detected in the thalamus [1], specifically in the lateral geniculate nucleus (LGN) [32] and thereby it is possible that picrotoxin is altering inhibitory processes at this first relay station point. This may also be the case with other brain systems responsible for the generation of secondary components, as GABA is somewhat ubiquitous. Alterations in the requisite inhibition necessary for recurrent time-related events to occur in the LGN may be disrupted by picrotoxin and thereby altering the VER. Thus, with at least these two considerations in mind, amplitude suppression of P1N1 may represent a partial effect on the transmission input (retinal or optic nerve) and/or at the first relay stage.

Strychnine

Generally, P1, N1 and P2 latencies were reliably shortened, however N3 latency was significantly increased. Only P3N3 amplitude was reliably altered and it was suppressed. Strychnine effects may also come via a two stage process. Strychnine is a known glycine antagonist [39]. Glycine has been reported to be involved in retinal transmission [15,24], specifically as an inhibitory transmitter as its intravitreal injection depresses ERG's and the early components of VERs in rabbits. Thus, the shortened delay of the initial VER components in the present study may be a partial result of increased retinal excitation via a strychnine induced glycine inhibition. The fact that strychnine shortened peak latency times while picrotoxin increased latencies suggests that the alteration of glycine and GABA, respectively, has differential effects on neural transmission in the visual system rather than any uniform action following a general release from inhibition, if indeed, the reasons for the convulsant modulation of the early components is retinal dependent. While glycine is being cautiously accepted as an inhibitory neurotransmitter, particularly of interneurons within the brain stem and spinal cord [39] no definitive study exists for its role in the LGN although thalamic neurons are known to be sensitive to local application of glycine [3]. Since the N3 component develops partially as a result of rebound excitation at the geniculate level, it is likely that suppression of P3N3 amplitude and the delay of N3 latency is due to a disruption in the inhibitory mechanisms of rebound excitation. Whether this is a direct or indirect effect is unknown. In related work [5,17], strychnine was found to completely block the development of ADs. Thus, the implication is that there may be partial glycine involvement with respect to inhibition in the LGN.

Physostigmine

In general, physostigmine attenuated the amplitude of all components except P2N2 and N2P3 but only caused an increase in delays for the P2 and P3 components. On some relay geniculate cells physostigmine evokes an increase in spontaneous firing rate (Bigler, unpublished observations) as well as an increase in discharge rate to a single afferent

volley [33]. As such the suppression of VER amplitude may come via an occlusion effect of increased background activity in the geniculo-cortical system, by keeping synchronous discharges slightly out of phase. This effect may also be tenable for any pharmacological agent that increases background firing rate and this needs to be considered as another possible explanation for the effects of strychnine or picrotoxin. There are also cholinergic pathways projecting from the midbrain to LGN [25,38] as well as other thalamic nuclei important in LGN modulation.

Metrazol

In general, Metrazol was essentially ineffective in altering the cortical VER in the present study even though Metrazol has reliable effects on ADs [6]. The effects of Metrazol thus have a dissociative action in that the primary and secondary VER components may not be directly affected while the AD may be markedly potentiated. This does support previous data that augmentation of AD is independent of effects at the primary component level [7]. In some preparations Metrazol mimics the effects of picrotoxin presumably because of their communality in affecting GABA inhibition [31]. As can be observed from the present data, Metrazol did not mimic the effects of picrotoxin, thus suggesting differential modes of action between these agents on the VER.

General Comment

It is axiomatic in neuropharmacology that no drug has a purely isolated neural action, but rather a primary action with side effects. This is undoubtedly the case with all of the agents used in the present experiment. Thus, even though all four convulsants could be distinguished and differentiated by their actions on VER components, the differences were probably not specific to single differences in mode of action. Since the animals utilized were unanesthetized preparations, one drug action of all these agents that needs to be considered is the corresponding alterations in "arousal level" of the animal following convulsant administration. By their nature of action all of these convulsants may alter arousal [6] and alterations in arousal level are known to change VER components, particularly late components [9,34]. However, the doses utilized in the present experiment were subconvulsive and recent experiments [6] have generally confirmed the essence of the above findings in urethane anesthetized rats in which "arousal level" would be controlled for by the anesthetic state.

It needs to be noted that there was some variability in the saline control with P1 and N3 peak latency and P3N3 amplitude being affected. The explanation of the significant variance in the P3N3 components can be readily ascribed to habituation effects which have been repeatedly demonstrated [2, 8, 34]. Explanation for the shortened P1 latency cannot be made so perfunctorily. Picrotoxin reliably delayed this component, the opposite action being found in the saline and strychnine conditions. However, the strychnine related decreases in peak latencies remained significantly intact across both N1 and P2 whereas saline had no effect on waves following P1. Accordingly, it is suggested that the significant result with saline on the P1 component is a spurious relationship. Likewise, in related work we have found, both in behavioral and pharmacological experiments, P1 latency to remain unchanged during saline and other controls [7, 9, 18].

As with the VER AD, the present data provide heuristic bases for differentiating the pharmacological actions of convulsants. In terms of the visual system evoked potential it appears most profitable at this time to explore the possible retinal effects as opposed to the more central actions of strychnine and picrotoxin. Also, it would be worthwhile to determine if anticonvulsant effects are likewise maintained in visual system evoked response analysis as they are with VER ADs [37].

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