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Pharmacologic Analysis of the Postictal Immobility Syndrome in the Rat

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MYSLOBODSKY, M. S., M. MINTZ AND O. KOFMAN. *Pharmacologic analysis of the postictal immobility syndrome in the rat.* PHARMAC. BIOCHEM. BEHAV. 15(1) 93–100, 1981.—Postictal immobility (PI) following chemically (picrotoxin, metrazol) and electrically-induced (maximal electroshock, MES) convulsions has behavioral features close to neuroleptic-type catalepsy. EEG, monitored postictally, showed that catalepsy is accompanied by a variety of EEG patterns. Cataleptic behavior extended beyond the period of "postictal EEG depression". During PI rats had vivid righting and corneal reflexes. Like haloperidol-pretreated rats they were able to maintain uncomfortable postures on the vertical grid or horizontal bar; although signs of rigidity were noticed, the rats would fail to remain self-supporting when placed across metal bookends ("bridge" test). All rats reacted to the tail-pinch immediately when the seizure would halt. However, 10–15 min later when PI was minimal or not detectable, animals became totally unresponsive to pressure applied to the tail ("delayed analgesia"). Examination of VEP recovery after MES showed that the secondary slow negativity and sensory afterdischarge were well developed irrespective of the score of the tail-pinch test. Pharmacological profile of PI suggests that the endogenous opiate system might contribute to this syndrome. Similar to morphine-induced catalepsy/catatonia: (1) PI is insensitive to atropine and scopolamine; (2) neither haloperidol nor alpha-methyl-p-tyrosine was able to potentiate it; (3) PI is reduced by apomorphine, naloxone, and physostigmine. Also, drugs acting via GABA system (γ-vinyl GABA, diazepam, sodium valproate) reduce PI intensity. It is hypothesized that PI system (1) is controlled by GABA carrying fibers and (2) uses neuropeptide with neuroleptic properties.

Postictal behavior Catatonia/catalepsy Analgesia EEG depression Chemically-induced convulsions Maximal electroshock

THE termination of a full-blown tonic-clonic convulsion leaves an animal temporarily torpid (behaviorally comatose, depressed, paralysed) with drastically reduced responsiveness to environmental stimuli. The mechanisms contributing to this phenomenon are not clear. A state of "neuronal exhaustion" (inactivation) may underly some but not all aspects of this syndrome as the immobility may be terminated in its incipience which reportedly would lead to agitated fearful behavior of the animal [31].

The belief that the primary disturbance in postictal period is chemical in nature has long been plausible [3]; that it is a disturbance of neurochemical functions is supported by observations that electrographic postictal depression and postictal behavior can be modified by drugs which act through the DA and GABAergic systems [25, 27, 28]. Also, there are indications that the postictal immobility may be associated with the hyperactivity of the system of endogenous opioids [17,34].

Two major types of behavioral syndrome may be hidden behind this postictal torpidity; rigid-catatonic and flaccid-cataleptic conditions, both suggesting involvement of extrapyramidal mechanisms. Although "catatonia" and "catalepsy" are often used interchangeably they have dissimilar behavioral profiles and imply different categories of participating transmitters systems [2, 4, 8, 30]. If postictal immobility is looked upon as either of these two behavioral syndromes, a further implication might be the narrowing of the area of search for the hypothetical sites (transmitter systems) contributing to postictal immobility, to either a system causing opiate-type rigid catatonia or neuroleptic-type catalepsy. Early observation on postparoxismal inhibition in rats after audiogenic and electroshock seizures showed that behavioral symptoms resembled those of "decerebrated rigidity" albeit animals were sensitive to pain [29]. As this syndrome does not fit well either neuroleptic-type catalepsy or opiate-rigidity [2], a further investigation of postictal effects is advisable.

The present study examines the possibility that certain known or unknown neuropeptides (the "acroagonines" of Cerletti [3]) are implicated in the postictal behavioral quiescence. The present communication primarily deals with behavioral aspects of postictal immobility and its sensitivity to a number of centrally active compounds. Observations on EEG during the immobility are also presented.

METHOD

Subjects and Materials

Experiments were performed on adult naive female and male Wistar rats (150–200 g) maintained under controlled experimental conditions with 12 hr light-dark cycle. Rats were pretreated with one of the following drugs: saline,

γ-vinyl GABA (GVG, Merrell International), sodium valproate (Reckitt-Labaz), diazepam (Assia), α-methyl-p-tyrosine (αMpT, Merck Sharp and Dohme), haloperidol HCl (McNeil), apomorphine HCl (Sandoz), atropine sulphate (Assia), physostigimine salicylate (Sigma), naloxone HCl (Endo), and Ro 5-3663 (Hoffman-La Roche). Each drug was injected IP in equal volume amounts. All doses (see Table 2) are expressed in terms of the salts. Convulsions were induced at about 4 hr after GVG, 3 hr after sodium valproate, 2 hr after αMpT, 30 min after diazepam and haloperidol, 15–20 min after apomorphine, atropine and physostigmine, and 2–3 min after Ro 5-3663 administration.

Surgery

Ten rats were anesthesized with nembutal and placed in a Kopf stereotaxic instrument. Two holes for recording electrodes located over symmetrical points of the visual cortex at a position 7.0 mm posterior to the bregma and ±3.0 mm from the midline were drilled with precautions taken to avoid dura damage. Two holes for anchoring stainless steel jeweller's screws were drilled on the midline over the frontal cortex and over the cerebellum. An additional hole for an indifferent electrode was drilled over the cerebellum on the midline. The cortical and indifferent electrodes were silver balls presoldered to Amphenol microminiature pins.

Epilepsy Models

Seizures were activated chemically with either picrotoxin (3–4 mg/kg) (Sigma), or metrazol (30–50 mg/kg) (Assia), as described elsewhere [24, 25, 27]. In several experiments electrically-induced seizures (maximal electroshock, MES) were examined. Shocks were delivered bilaterally from a Grass S48 stimulator, through intra-aural electrodes. The parameters of 2 sec train of rectangular pulses were: 110 V, 0.1 msec, 60 Hz.

Behavioral Tests

Rats were placed individually in open rectangular plastic boxes (45×30×13 cm) for continuous observation of seizure development, gross abnormalities of behavior, responses to noxious stimuli (tail-pinch agitation test) and corneal reflexes. The tail-pinch response was rated on a semiquantitative scale of 0 to 3 as absent (0), present (1) when a clearly detectable forward motion was emitted unaccompanied by a jerk, and moderate (2) when a clear forward or lateral avoidance response with vocalisation was emitted. The response was rated as strong (3) when the rat produced a tight deviation toward the tail accompanied by a squeak. This was a typical response to the painful tail-pinch in normal rats [26].

Rigidity was inspected by handling the rat and assessed on the basis of the results of the "bridge" test: a positive score required that the rat remain self-supporting for 10 sec when placed across metal bookends [2]. Catalepsy was evaluated by placing the rat on the vertical grid or the horizontal bar [8,30]. The intensity of the response was rated on a scale reflecting the time that the rat remained on the grid or the bar (1—not less than 15 sec, 2 and 3—immobility for not less than 30 and 60 sec, respectively).

Behavioral tests were also conducted during EEG and visual evoked potentials (VEP) recording sessions in the experimental cage (Fig. 1). Rats were taken to the experiment five–seven days after surgery. EEG was recorded with a Beckman Type R machine (bandwidth 0.53–30 Hz). A swivel, mounted on the top of the cage, provided artifact-free EEG recording in unrestrained rats. VEPs were recorded monopolarly against a reference electrode positioned over the cerebellum. A 10 μsec flash (intensity 8, Grass PS 22 photostimulator) was delivered randomly with an interval not less than 3 sec on the artifact-free EEG background. Mirror walls of the electrostatically shielded cage secured that the retina was illuminated irrespective of the rat's position. Blocks of 20 VEPs were averaged by PDP-8 minicomputer and plotted on a paper by X-Y plotter (Hewlett-Packard 7035 B). All tests were conducted in a counterbalanced fashion between 9:00 and 15:00.

TABLE 1

EFFECT OF DRUGS ON THE TAIL-PINCH SCORE (MEAN ± S.E.M.) DURING POSTICTAL IMMOBILITY INDUCED BY METRAZOL, PICROTOXIN OR MAXIMAL ELECTROSHOCK

Pretreatment (dose)	Picrotoxin	Metrazol	MES
Saline 0.9%	1.0 ± 0.18 (8)	1.4 ± 0.22 (5)	1.5 ± 0.18 (8)
GVG (1000 mg/kg)	1.8 ± 0.18 (5)	1.6 ± 0.22 (5)	1.3 ± 0.25 (4)
Sodium valproate (300 mg/kg)	1.8 ± 0.20 (n=5)	1.25 ± 0.25 (n=4)	not tested
Haloperidol (0.25 mg/kg)	1.4 ± 0.30 (7)	1.8 ± 0.18 (5)	1.5 ± 0.28 (3)
αMpT (200 mg/kg)	1.3 ± 0.34 (3)	1.3 ± 0.34 (3)	1.7 ± 0.28 (3)
Physostigmine (0.1 mg/kg)	1.2 ± 0.25 (4)	1.7 ± 0.25 (5)	not tested
Atropine (1 mg/kg)	1.7 ± 0.17 (3)	1.7 ± 0.17 (3)	not tested
Ro 5-3663 (2 mg/kg)	not tested	not tested	1.8 ± 0.29 (8)

Analysis of Data

For each of the convulsant conditions (picrotoxin, metrazol and MES) and drug effects, a separate mean±S.E.M. was computed. The analysis of variance (ANOVA) for unequal groups was carried out. A rejection region was selected at $p<0.001$.

RESULTS

General

The results of behavioral experiments demonstrate that during postictal immobility all rats showed vivid corneal and righting reflexes and shared reproducible behavioral patterns, irrespective of the convulsant employed.

Placed on the horizontal bar or on the vertical grid, the rats would remain in uncomfortable postures for at least 15–60 sec or longer. While signs of rigidity may be noticed during handling, especially in the MES condition, the rats would typically fail a more demanding rigidity test ("bridge" test).

The cataleptic features of behaviour typically required about 20–40 sec to develop. If tested earlier, the animals

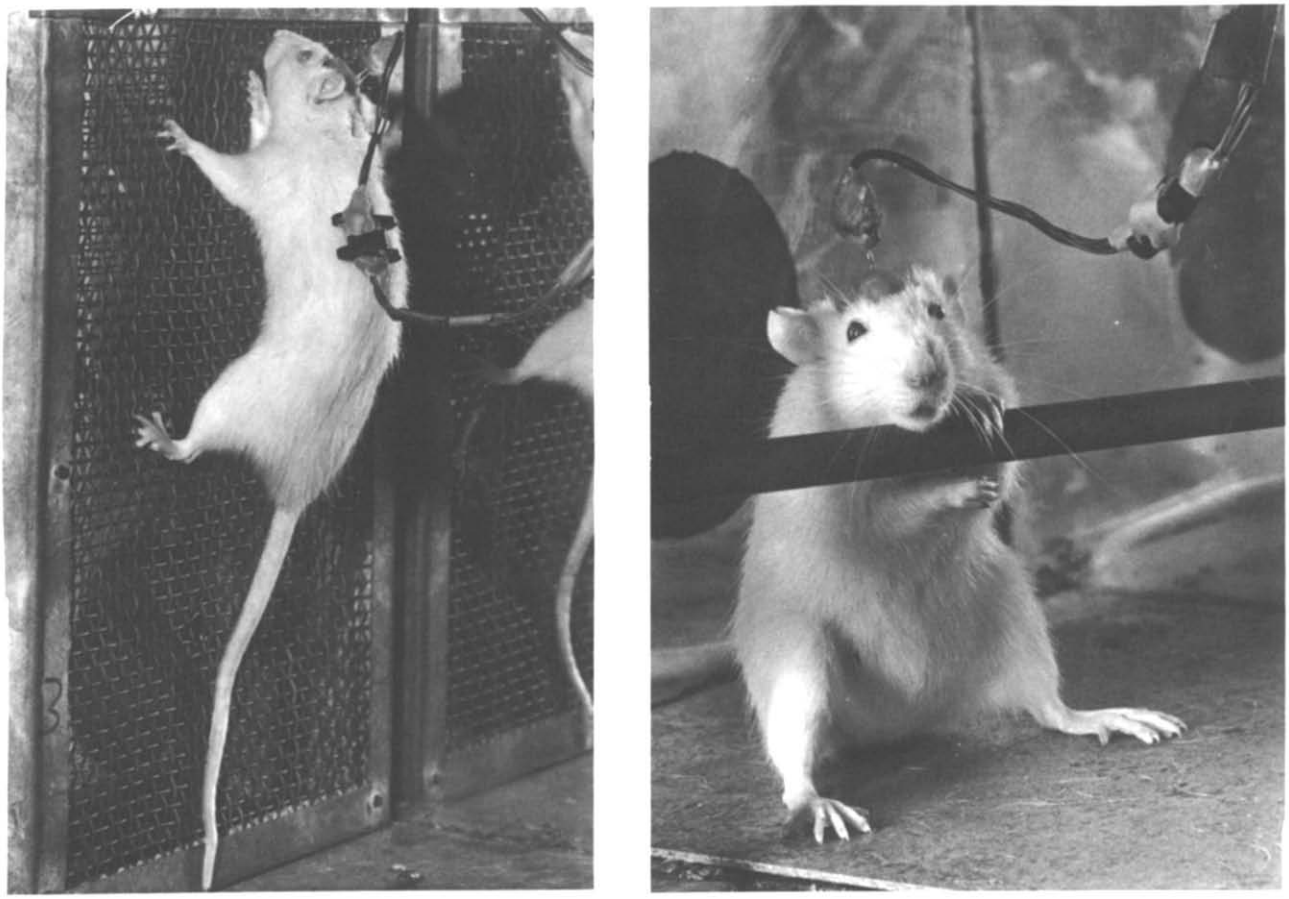

FIG. 1. Examples of cataleptic behaviour during EEG examination. Left, a typical posture on the vertical metal grid; right, an immobile rat on the horizontal bar.

would passively "hang" rather than support themselves on the bar and would slide off the grid.

All rats showed reaction to the tail-pinch as soon as seizure would halt. A low score of the response indicates that the rat, although squeaking, seldom exhibited a tight deviation of the body or circling movement toward the tail, as a normal rat typically does [26]. It is important to add that the tail-pinch reaction was maximal within about one min after seizure (values in Table 1 reflect this period), while 5 min later the intensity of the reaction already began to decrease and by 10–15 min, when catalepsy was either reduced or vanished, the pressure applied to the tail would leave the rat totally unresponsive. This phenomenon was designated "delayed analgesia".

When food pellets were placed on the floor of the cage during the testing, the tail-pinch produced voracious eating in 90% of animals.

Convulsant-Specific Effects

Notable differences of behavioral profiles were observed. Metrazol caused less consistent performance on the vertical grid since the rats would often slide off the grid after small residual postictal jerks. Similar jerks after picrotoxin seldom interfered with the rats' performance, unless a full-blown secondary seizure developed. Interestingly, only in the picrotoxin condition, the positioning of the rat on the vertical grid often activated a secondary seizure. Unlike metrazol or MES, post-picrotoxin immobility showed oral dyskinetic symptomatology (chewing, gnawing), but the tail-pressure induced eating was a rare event in this condition.

After the MES, rats had mild exophthalmus and clearly delayed righting reflex, even though they had normal corneal reflex and reacted vigorously to the tail-pinch in the incipience of immobility. In two rats signs of rigidity were noted in the form of Straub tail and the clasping of limbs to the body when suspended by the tail. Only in the MES condition was catalepsy sometimes superceded or accompanied by the postictal explosive behavior. This behavior was strikingly similar to that developing after amygdaloid kindling of epilepsy where it was designated as "postictal excitation" [27].

Electrophysiological Findings

Each rat was gently placed on the bar or the grid as soon as the seizure after-discharge came to a halt (Fig. 1). The records obtained showed that postictal electrical depression

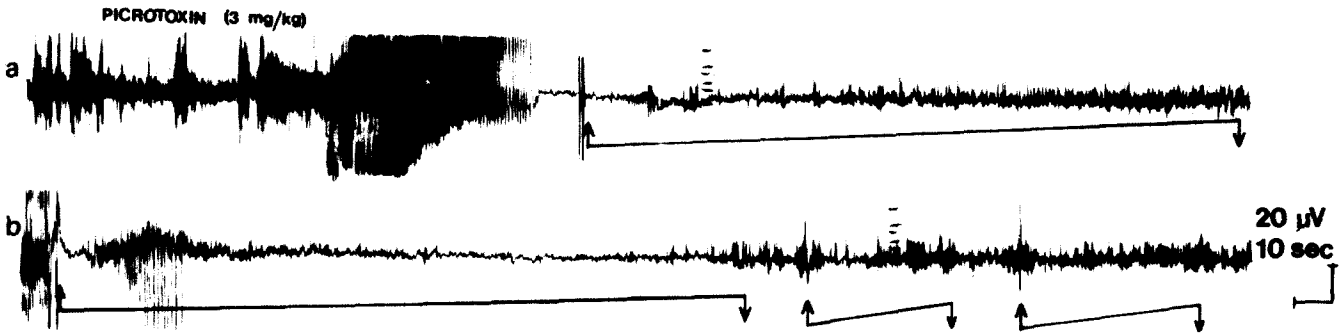

FIG. 2. Picrotoxin-induced seizures. Records were taken from two different experiments. In both (a) and (b) the rat was placed on the bar at the first "on" arrow, right after the seizure afterdischarge came to a halt. "Off" arrow joined with "on" arrow by lines denotes the end of the test when the rat leaves the bar. In the last (third) test of the fragment (b) the rat was positioned on the grid.

is not the major correlate of immobility. The rats would remain on the bar longer than the postictal EEG flattening lasted (Fig. 2). The ability of the rats to remain on the grid was best at the end of postictal depression, when the hypersynchronized 3–5 Hz wave-spike patterns superceded postictal EEG flattening. However, this pattern remained when catalepsy was absent or barely detectable. We failed to detect any particular EEG pattern which may be correlated with, or signal the development or cessation of catalepsy. Also, no specific EEG pattern was noticed to correlate with delayed analgesia.

To further assess postictal brain reactivity, the recovery of VEP was examined and compared with the scores of the tail-pinch test. This study was confined to the MES condition, as chemical convulsants invariably contaminate the recovery process.

Figure 3 (the top trace) shows a typical VEP pre-seizure pattern. It is composed of unstable primary complex, followed by a series of secondary waves. Notably, a prominent slow secondary wave (peak latency about 150 msec) as well as oscillations of the secondary afterdischarge are well represented. The presence of these components indicates that VEP was recorded in a state of reduced arousal, as both the slow negativity and afterdischarge are known to undergo suppression when noxious or arousal-inducing conditioned or unconditioned stimuli are inflicted (see [24] for review). The changes of these VEP components were expected to assist in detecting the time-course of analgesia and in assessing (even if roughly) its intensity. Indeed, typically the slow negativity was more pronounced during delayed analgesia. Puzzlingly, however, this VEP component was also well developed when the tail pressure scores were high. Figure 3 shows that the slow negativity and afterdischarge were not suppressed either during explosive behavior (an inconceivable finding in normal animal) nor during recovered sensitivity to tail pressure (scores 2–3).

Group findings have shown (Fig. 4) that the amplitude of the slow negativity is greatly reduced even after sham MES, which consisted of restraining the rat and attaching the electrodes. As a result of the sensitivity of this component, the MES-induced suppression of the VEP did not differ significantly from the corresponding sham MES values. In contrast, a consistent increase of the slow negativity peak la-

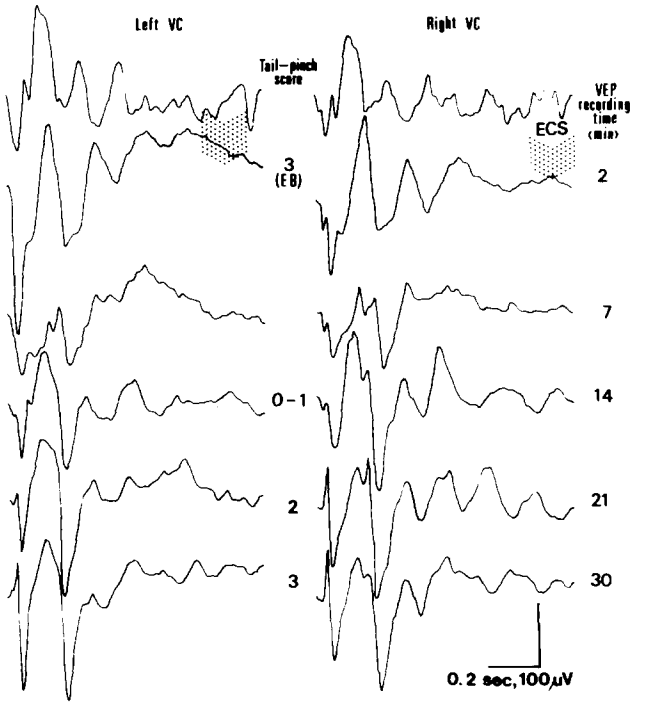

FIG. 3. Average VEP in a rat after bilateral electroconvulsive shock (ECS) showing changes during different recording sessions. The second and subsequent traces are taken after ECS. The top trace represents the baseline VEP of a relaxed animal. Note that the secondary VEP components remain fairly pronounced during explosive behavior (EB) and maximal scores of the tail-pinch test. Each trace is an average of 20 artifact-free potentials. Negativity of the active electrode is upwards. The presentation of the stimulus coincides with the beginning of the curve.

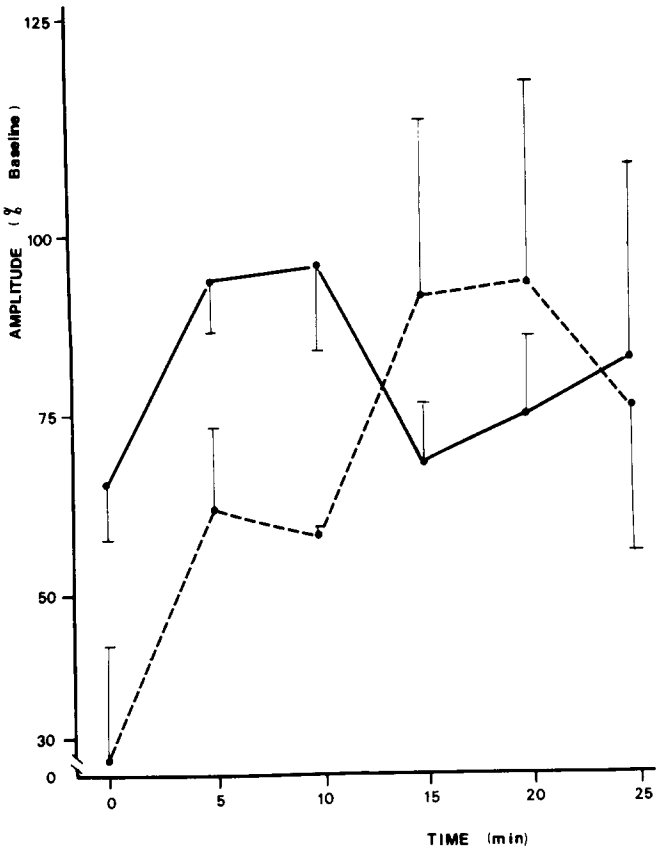

FIG. 4. Mean amplitude of the slow negative wave (± SEM) of VEP as a function of time after MES (interrupted line) or sham MES (solid line). Sham MES consisted of restraining the rat and attaching electrodes. Each value represents the percent change (N=3–4 experiment/point) from the background value. VEP averaging was initiated at 0–2 min after seizure. Each subsequent average was taken at the time indicated ±1 min.

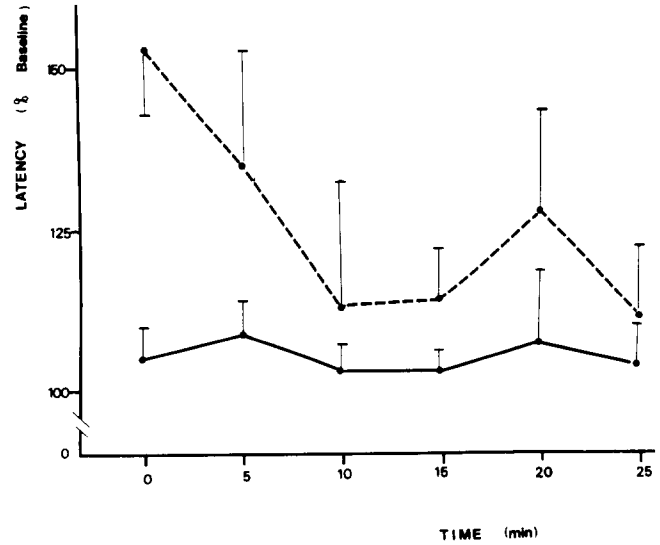

FIG. 5. Mean peak latency of the slow negative wave (±SEM) of VEP as a function of time after MES (interrupted line) or sham MES (solid line). Each value represents change (N=3–4 experiment/point) from background value. (Time base as explained in Fig. 4.)

TABLE 2

ACUTE EFFECTS OF SYSTEMICALLY ADMINISTERED DRUGS ON POSTICTAL CATALEPSY CAUSED BY PICROTOXIN, METRAZOL AND MAXIMAL ELECTROSHOCK (MES)

Pretreatment (dose)	Challenge	N	Vertical Grid	Horizontal Bar
None	Picrotoxin	5	2.2 ± 0.19	2.6 ± 0.24
	Metrazol	5	2.2 ± 0.11	2.8 ± 0.11
	MES	4	3.0	2.8 ± 0.30
GVG	Picrotoxin	5	2.0 ± 0.62	2.4 ± 0.58
(1000 mg/kg)	Metrazol	5	1.4 ± 0.22	2.4 ± 0.22
	MES	4	1.5 ± 0.25*	1.8 ± 0.30
Sodium valproate	Picrotoxin	5	2.2 ± 0.37	2.8 ± 0.20
(300 mg/kg)	Metrazol	4	1.5 ± 0.25*	1.8 ± 0.25*
Diazepam	Picrotoxin	4	†2.5 ± 0.28	†2.0 ± 0.40
(5 mg/kg)	Metrazol	3	0*	0.3 ± 0.32*
Haloperidol	Picrotoxin	7	2.6 ± 0.19	3.0
(0.25 mg/kg)	Metrazol	5	2.6 ± 0.22	2.6 ± 0.22
	MES	3	2.3 ± 0.28	3.0
αMpT	Picrotoxin	3	3.0	3.0
(200 mg/kg)	Metrazol	3	2.3 ± 0.34	3.0
	MES	3	2.3 ± 0.28	3.0
Physostigmine	Picrotoxin	5	1.2 ± 0.37	2.0 ± 0.70
(0.1 mg/kg)	Metrazol	4	0.5 ± 0.28*	1.8 ± 0.25*
	MES	3	2.6 ± 0.33	2.0 ± 0.57
Atropine‡	Picrotoxin	3	3.0	3.0
(1 mg/kg)	Metrazol	3	2.6 ± 0.32	3.0
	MES	4	3.0	3.0
Apomorphine	Picrotoxin	4	2.0 ± 0.57	2.3 ± 0.25
(10 mg/kg)	MES	4	2.2 ± 0.25	1.0 ± 0.40
Naloxone	Picrotoxin	5	2.2 ± 0.19	2.4 ± 0.24
(10 mg/kg)	MES	3	2.7 ± 0.32	3.0
Ro 5-3663	MES	8	2.7 ± 0.16	1.8 ± 0.39
(2 mg/kg)				

Values represent the mean group score (± S.E.M.).

*Values significantly different from respective convulsants alone at $p<0.001$. Differences between the cataleptic scores in picrotoxin and metrazol seizure conditions are denoted by the vertical line and a symbol †$p<0.001$ (two-tailed).

‡In the maximal electroshock condition rats were pretreated with scopolamine (1 mg/kg).

tency following MES (Fig. 5) was significantly different, $t(6)=4.118$; $p<0.01$, two-tailed, from the corresponding sham MES values immediately after the seizure (at 0 point).

Pharmacologic Profile of Postictal Immobility

Several drugs acting via dissimilar transmitter systems altered the pattern of postictal behaviors. Their effects varied in intensity among different convulsions, as shown in Table 2. The picrotoxin condition was the least sensitive and the metrazol condition the most sensitive to the action of the drugs tested. A comment regarding some drug effects is provided below.

Haloperidol. The most surprising observation was that the drug which in a dose of 2 mg/kg caused profound catalepsy, did not intensify postictal immobility within 2–5 min after the seizure ended. A subcataleptic dose (0.25 mg/kg) failed to affect postictal behavior in any appreciable

way. Interestingly, this dose of haloperidol caused a mild catalepsy when a subconvulsive dose (2 mg/kg) of picrotoxin was administered (the score on the grid was 2.0 ± 0.70, and 1.4 ± 0.54 on the horizontal bar). Also, after a convulsive dose of picrotoxin, haloperidol-induced catalepsy was pronounced during the "sedation stage" [27] of picrotoxin effect. This notwithstanding, postictal performance in this test remained unaffected.

Apomorphine and naloxone. Both compounds remarkably shortened the duration of immobility which in the MES condition was followed by a period of excitation with jumping and fearful-aggressive behavior. Apomorphine in addition reduced the intensity of cataleptic behavior, albeit not significantly so. In both conditions the immobility period was so shortened that the catalepsy tests were conducted only once.

None of the drugs affected the delayed analgesia. Even a large dose of naloxone (20–70 mg/kg) which activated lethal seizures in a few animals when administered in the immobility period, did not reverse analgesia. Pressure applied to the rats' tail may cause walking or squeaking, escape maneuvers with biting of any object placed in front of the animal, but the rat would never produce the pain-directed rotational response.

GVG, sodium valproate and diazepam. These substances tended to reduce cataleptic symptomatology. The effect was most pronounced in the metrazol condition and practically absent in the picrotoxin condition. GVG also increased the duration of the period of poor righting reflex and entirely eliminated postictal explosive behavior after MES, as has been noted in kindled epilepsy [28].

Physostigmine. This drug reduced cataleptic symptoms albeit largely in the metrazol condition, while αMpT, atropine (or scopolamine) did not alter rats' behaviors.

Ro 5-3663. Convulsant benzodiazepine, Ro 5-3663 was tested only in conjunction with MES. Given before or immediately after seizure in a dose of 2 mg/kg this compound reduced the intensity of delayed analgesia.

DISCUSSION

The findings of the present study clearly demonstrates that although postictal reduced responsiveness and immobility may overlap with postictal flattening of EEG, the processes of cellular inactivation underlying postictal depression hardly contribute to postictal catalepsy. The latter did not seem to correlate with any specific EEG pattern. VEP analysis adds an intriguing feature to the seemingly behavior-independent process of EEG recovery. We refer to the lack of correspondence between the sensitivity to tail pressure or the intensity of aggressive-fearful behavior, and the amplitude of secondary VEP components. This is clearly a postictal phenomenon, as in normal animals there is an inverse relation between the amplitude of secondary VEP components and pain and/or arousal-related locomotion [24]. It may suggest that the cortex is partially and selectively functionally isolated from some of its inputs, which normally modulate its responsiveness. We do not have an adequate explanation for this effect. Further studies of brain reactivity would be useful in order to obtain a more complete picture of cerebral (neocortical) excitability changes during postictal catalepsy.

A fairly plausible analogy which offers itself is that postictal immobility (at least after chemically-induced convulsions) is related more to neuroleptic-type catalepsy, rather than to opiate-type rigid catatonia. However, a delayed postictal analgesia and the pharmacological profile of this syndrome may favor the idea of the significant endogenous opiate involvement. In fact, the failure of the anticholinergic drugs to antagonise immobility is compatible with this idea, as atropine and scopolamine, which readily antagonize haloperidol-induced catalepsy, do not prevent morphine or methadone-induced catalepsy/catatonia [10,22]. Also, apomorphine which is known to antagonise morphine-induced catatonia, but not neuroleptic-induced catalepsy [10] antagonised postictal immobility.

A considerable delay of analgesia development may be associated with a non-synaptic release of endogenous opiates. Dunn [9] has recently hypothesized that the cerebrospinal fluid may serve as a vehicle for transmitting neuropeptides from their release sites to target cells. While it may be required that this hypothetical peptide should not be readily degraded to account for both the analgesia delay and its considerable length, intracerebral administration of β-endorphine has reportedly produced electrographic seizures followed by a delayed (20–30 min) analgesia [16].

The low sensitivity of delayed analgesia to naloxone seems puzzling and may suggest that non-opiate analgesic systems are involved. In this respect the Ro 5-3663 effects are intriguing. Given the possibility that this compound is mimicking a natural ligand for the benzodiazepine receptor [33] these findings may implicate GABA or/and benzodiazepine-mediated mechanisms in PI analgesia. However, it is known that opiate antagonists do *not* necessarily inhibit every action of endogenous opiates or narcotics [6]. A typical example is naloxone inability to antagonise postictal catalepsy which may be associated with a slight cataleptogenic action of this drug [22]. Also, given that after naloxone administration some components of reaction to pain were present, this finding invites a more parsimonious explanation. It has been demonstrated that postural and circling components of the tail-pinch reaction are most closely related to the rats' rotation behavior under amphetamine [26]. This particular component of the response may be selectively inhibited by the system bringing catalepsy to the fore, which disrupts routinized sensory-motor patterns of behavioral response to pain. In fact, if during testing food pellets were available in the vicinity of the rat, the tail-pinch would produce a voracious eating response in the otherwise immobile animal.

Another important aspect of the present findings suggests that the nature of postictal immobility may vary in seizures of different origins. At least the MES-caused immobility with delayed righting reflex, exophthalmus, signs of rigidity and occasional postictal excitation—especially striking when postictal immobility is eliminated with naloxone or apomorphine—suggests a possibility of β-endorphine involvement. However, the syndrome developing after MES also had typical features of catalepsy. While the lack of rigidity after chemically induced convulsions may be related to the ambiguity of the tests employed [4], an alternative possibility is that the postictal syndrome is caused by several neuropeptides, with one of them having largely neuroleptic properties, as has been postulated for stress producing events by Jacquet and Marks [19]. Since it has been contested by some writers [2], that β-endorphines do not possess these properties as Jacquet and Marks [19] have argued, a better candidate might be a peptide of des-tyrosine-γ-endorphine type, whose effects are reportedly strikingly

similar to haloperidol, and which does not act via dopamine receptors [7].

How, then, can one interpret the findings with GVG, diazepam and sodium valproate, all of which alleviate postictal catalepsy, implicating GABA in the behavioral torpidity control? The relationship between GABA and other neurotransmitters in the nigrostriatal system is the subject of considerable controversey. If the GABAergic channel originating in the caudate [11] and/or the globus pallidus [15] has inhibitory feedback functions on the nigro-striatal dopaminergic neurons [32], then elevation of GABA content in the brain after GVG administration, and, inter alia, in the nigro-striatal system, would be expected to increase dopamine-related catalepsy. In the present study GVG tended to cause reduction rather than enhancement of catalepsy in metrazol and maximal electroshock conditions but not after picrotoxin, antagonising GABAergic effects. Diazepam also showed a pronounced anticataleptic effect. Benzodiazepines are believed to facilitate GABAergic transmission removing the endogenous protein regulator from the high affinity GABA receptors [13]. A comparatively weaker action of GVG than of diazepam is probably related to the fact that this GABA-transaminase inhibitor given in a single dose did not produce a sufficient increase of GABA in nerve-terminal compartment [12]. In fact, the effects of sodium valproate, which is known to increase predominantly nerve-terminal GABA [12], have a pattern similar to GVG, but sodium valproate would alleviate postictal immobility (PI) more distinctly. Also, the anticataleptic effect of both sodium valproate and diazepam was more pronounced in the metrazol than in the picrotoxin conditions, which supports the notion that GABAergic mechanisms are involved in the postictal immobility control.

If GABA acts through the DA-containing neurons, then this evidence would suggest that GVG acts to potentiate the nigrostriatal impulse traffic activating the dopaminergic system, thereby reducing the intensity of PI. This conjecture, although in line with the findings that the net effect of GABA in the nigro-striatal dopaminergic pathway is excitatory [1], faces serious difficulties. A reduction of DA available at synaptic sites (with α-MpT) failed to increase PI. Also, haloperidol caused cataleptic symptomatology in the myoclonic stage (albeit again only in the picrotoxin condition) and was completely ineffective during PI. Both findings did not support a DA role in PI syndrome, although this evidence is insufficient to reject their contribution.

Worms *et al.* [35] have described a biphasic effect of picrotoxin which at low doses have significantly potentiated, and at high doses antagonised neuroleptic-induced catalepsy. Within the context of the present study the "low-dose effect" would probably correspond to the initial (myoclonic) stage of the haloperidol-picrotoxin interaction. In fact, doses of picrotoxin inducing jerks but not leading to a generalized fit (2 mg/kg) caused an identical effect (data not shown). The "high dose effect" would then correspond to the failure of haloperidol to potentiate postictal catalepsy. We have no explanation, at the present time, for the intriguing haloperidol-picrotoxin interaction. It does not seem likely that this interaction is associated with GABA agonistic properties of both haloperidol [18,20] and picrotoxin [27, 30, 35], as this combination did not mimic the effects of GVG and diazepam while the picrotoxin condition always tended to potentiate postictal catalepsy. Whatever explanation may emerge, the present evidence is interpreted as suggesting that GABA regulates postictal catalepsy via a system (not necessarily dopaminergic) which becomes disinhibited as soon as brain GABA is decreased by a seizure.

The effects of GABA do not exclude the contribution of the opiate system. Opiate receptors have been found in a number of brain regions rich in GABA, such as the nucleus caudatus and the globus pallidus [2]. Considering that enkephalines exert an inhibitory influence on the GABA neurons [22], it is likely that an increase of endorphines postictally may inhibit GABAergic inhibitory effects on the catalepsy system. It would be important to examine the possibility that GABA-carrying fibers control the mechanism of catalepsy, which uses a long-acting endogenous peptide with neuroleptic properties as one of its transmitters operating on DA-sensitive neurons in the neostriatum and amygdala. Given the systemic route of drug administration employed in the present study, it is advisable to abstain at this stage from ascribing the effects observed to any particular pathway or mechanism.

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