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Effects of Acute and Subacute Antidepressant Treatment on Kindled Seizures in Rats[1]

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KNOBLOCH, L. C., J. M. GOLDSTEIN AND J. B. MALICK. *Effects of acute and subacute antidepressant treatment on kindled seizures in rats.* PHARMAC. BIOCHEM. BEHAV. 17(3) 461–465, 1982.—The effects of acute and subacute administration of the tricyclic antidepressants imipramine and amitriptyline, and the atypical antidepressants mianserin and iprindole, on seizures kindled from the amygdala and the cortex were examined. Whereas amitriptyline selectively antagonized seizures kindled from the amygdala after a single dose, neither amitriptyline nor imipramine was any more effective in antagonizing seizures kindled from the amygdala than from the cortex following subacute treatment. Both acute and subacute administration of iprindole failed to significantly alter seizures kindled from either site. Although only the highest acute dose of mianserin tested selectively attenuated amygdaloid seizures, a lower dose that was ineffective when given acutely, was selective when given subacutely. In contrast to an earlier report, the present findings suggest that kindling may not be a particularly useful model for the evaluation of potential antidepressant agents.

Antidepressants Acute Subacute Seizures Amygdala Cortex

THE kindling phenomenon, originally developed and elaborated upon by Goddard and associates [8,9], is characterized by several overt behavioral manifestations of low intensity brain stimulation (LIBS). Although LIBS does not produce seizures upon initial exposure, they can be elicited from both a limbic site, the amygdala being the most responsive area, and a non-limbic site, such as the sensorimotor cortex, following repeated daily electrical stimulation (i.e., kindling).

Babington and Wedeking [2] investigated kindling as a model for the evaluation of potential antidepressant agents. The tricyclic antidepressants were reported to be more potent as antagonists of seizures kindled from the amygdala than from the cortex. The selectivity observed with the antidepressants was not observed with representative compounds from several other classes of CNS agents, such as anticonvulsants, neuroleptics, and anxiolytics. The anticonvulsants and anxiolytics produced a non-selective blockade of LIBS seizures (i.e., both amygdaloid and cortical seizures were blocked); the anxiolytics were more potent than the anticonvulsants. The neuroleptics, even in debilitating doses, did not block seizures kindled from the amygdala or the cortex. The selective blockade of amygdaloid seizures by antidepressants was a particularly exciting finding since the amygdala has long been believed to be the site of action of this class of psychotropic drugs [5, 7, 10, 11, 12, 13, 17].

The present studies were therefore undertaken to evaluate the effects of the tricyclic antidepressants imipramine and amitriptyline, and the atypical antidepressants mianserin and iprindole, on seizures elicited from both the amygdala and the cortex after both acute and subacute administration.

METHOD

Male Wistar rats weighing 200–220 g prior to surgery were used in the present studies. Each rat was housed individually in a controlled environment and maintained on an ad lib food and water regimen throughout the entire experiment. Under Nembutal (sodium pentobarbital) anesthesia (50 mg/kg), each rat was implanted stereotaxically with a stainless steel bipolar electrode (Plastic Products Co., Roanoke, VA; MS 303) in either the centromedial amygdala: 0.4 mm posterior to bregma, 5.0 mm lateral to the midline, and 9.0 mm below the surface of the skull [2], or in the sensorimotor cortex: 1.0 mm anterior to bregma, 3.5 mm lateral to the midline, and 2.3 mm below the surface of the skull [15].

With the exception of a few minor modifications, seizures were kindled by the procedure described in detail by Babington and Wedeking [2]. Two weeks following surgery, each rat was stimulated once daily for 1 min with a 50 μA, 60 Hz constant current sine wave (Lafayette Instrument Co., Lafayette, IN; Sine Wave Stimulator Model 82409). These 1 min stimulations continued only until bilateral clonic convulsions with consistent onsets and durations were established. Sensitization took about 30 days in the amygdala group, but as long as 60 days in the cortically-implanted group. Once each rat was kindled, the stimulus was applied only until the onset of a seizure (usually between 5 and 10 sec).

The effects of antidepressant drugs on the duration of seizures kindled from the amygdala and the cortex were then investigated. Prior to receiving drug, each rat received two

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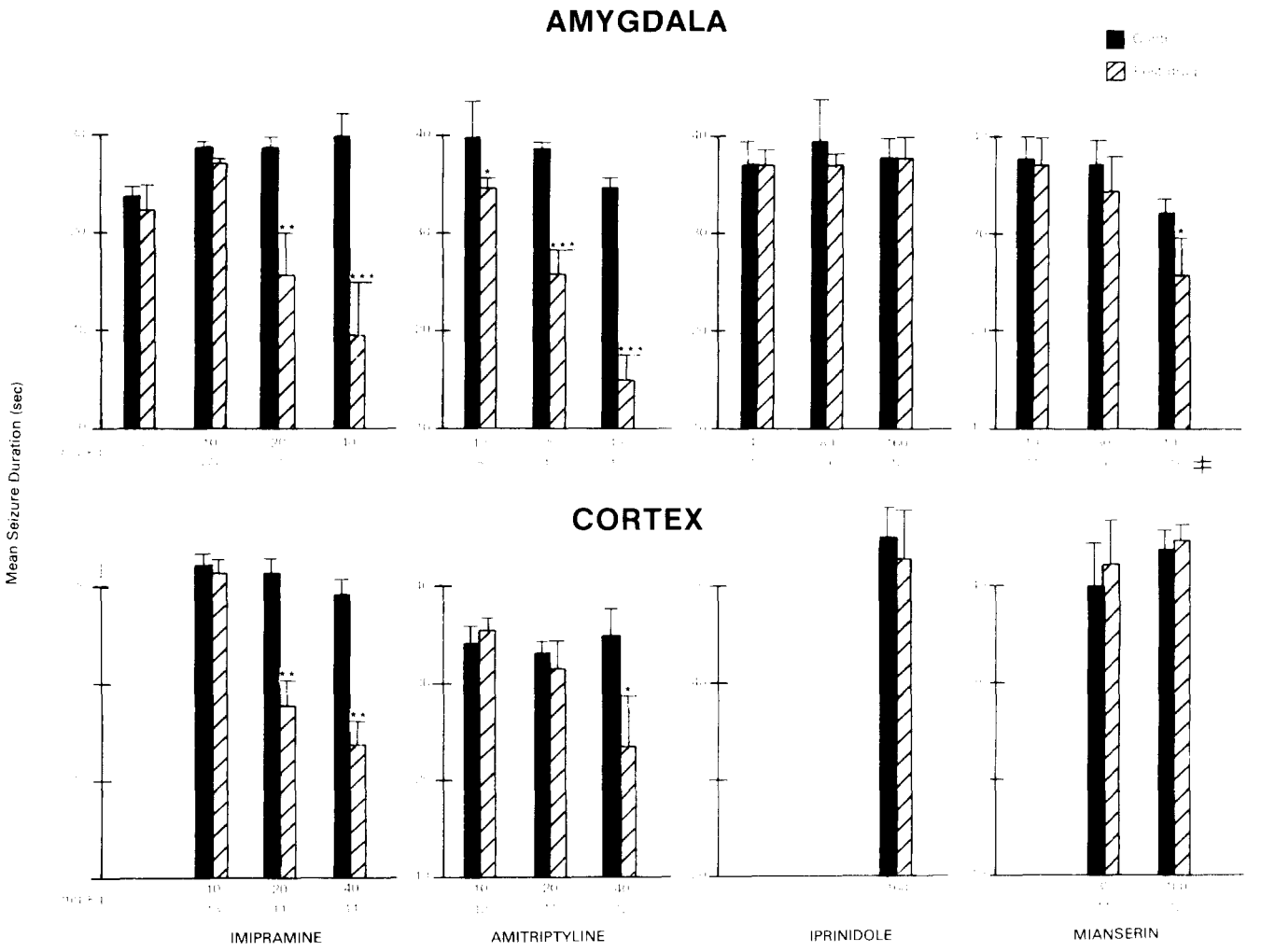

FIG. 1. Dose-response effects of acute imipramine, amitriptyline, iprindole and mianserin on the duration of kindled seizures from the amygdala and the cortex. *$p<0.05$, **$p<0.01$, ***$p<0.001$ Student's t-test for paired comparisons. ( )=Number of rats; ‡ represents data pooled over two experiments.

consecutive kindling trials 30 min apart in the amygdala group and 60 min apart in the cortical group (cortical animals could not be re-kindled when stimulated at less than 60 min between trials). The two control values were averaged together provided that the means of the trial durations were not significantly different (Student's t-test). Drugs were then administered either acutely (a single dose 30 min prior to testing once a week) or subacutely as three doses over a 24 hr period (24, 5 and 1 hr prior to testing) (2-day study), or three doses over a 24 hr period plus once daily for the next three days (5-day study). Testing following subacute administration was 1 hr after the last drug injection. All drugs were dissolved in 0.9% saline and injected intraperitoneally (IP) in a volume of 1 ml/kg. Acute drug effects were evaluated by comparing the mean pre-drug seizure duration to the mean post-drug seizure duration using the Student's t-test for paired comparisons; in each subacute study drug effects were evaluated using the respective mean pre-drug seizure duration obtained on day 1.

Following completion of the studies, rats were killed with an overdose of Nembutal, perfused with 0.9% saline followed by 10% formalin and the brains removed. Serial sections of brain tissue were cut on a cryostat and examined microscopically for electrode placement.

RESULTS

Histological examination of the brains of several rats revealed that electrodes were within the centromedial nucleus of the amygdala and the sensorimotor area of the cortex. Rats that were not sacrificed but used in the present studies had response patterns consistent with rats in which histological confirmation of electrode sites was made.

The stability of kindled seizure duration is illustrated in Table 1. There was very little variability in either amygdaloid or cortical seizure duration.

The effects of acute administration of both typical (amitriptyline, imipramine) and atypical (mianserin, iprindole)

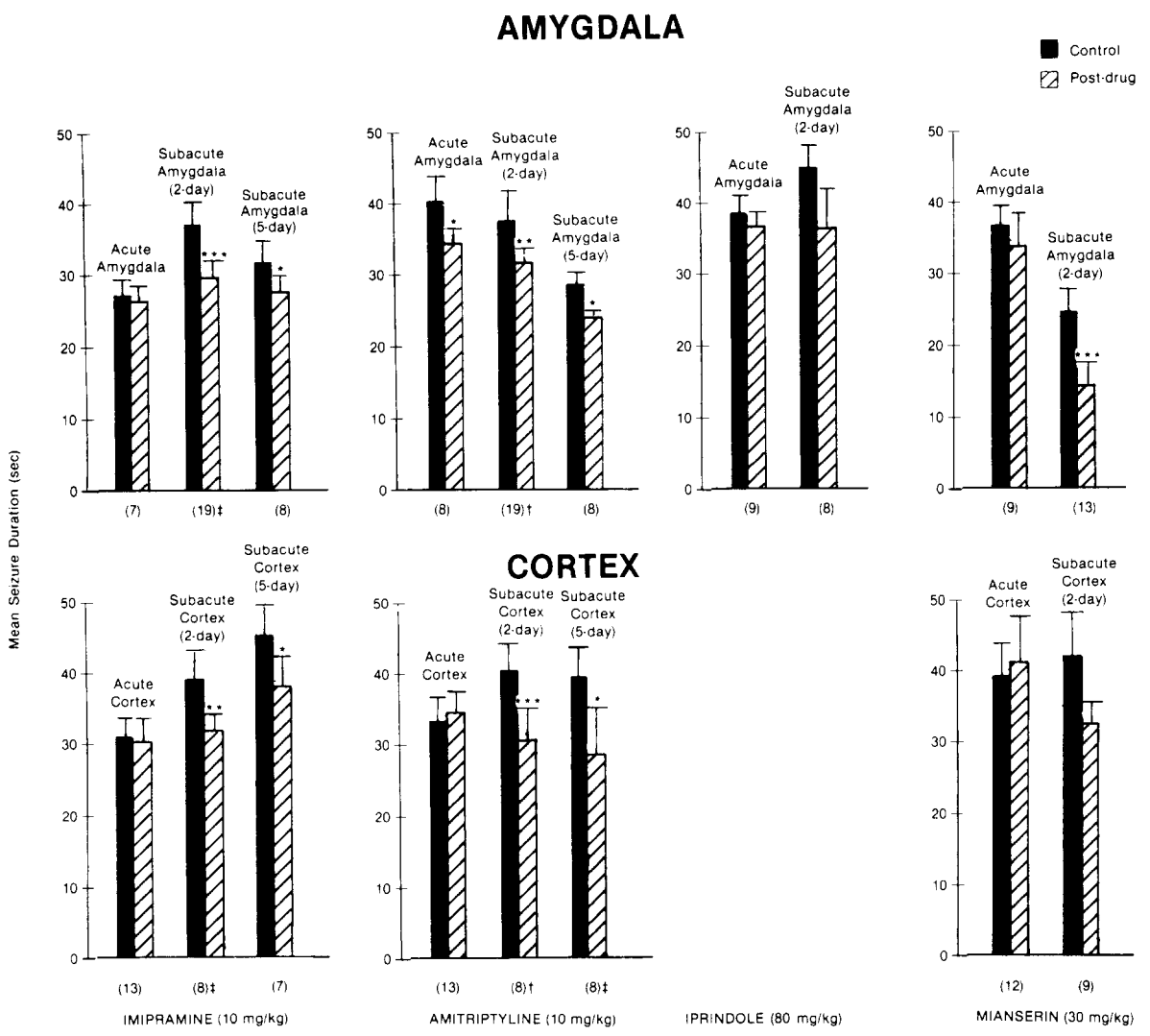

FIG. 2. Effects of acute and subacute (2-day and 5-day) imipramine, amitriptyline, iprindole and mianserin on the duration of kindled seizures from the amygdala and the cortex. $*p<0.05$, $**p<0.01$, $***p<0.001$ Student's t-test for paired comparisons. ( )=Number of rats; † represents data pooled over three experiments; ‡ represents data pooled over two experiments.

TABLE 1

STABILITY OF KINDLED SEIZURE DURATION

Stimulation Site	N	Mean Seizure Duration (±SE)	Number Days Between Kindling Trials
Amygdala	7	28.0 ± 1.2	0
	7	28.0 ± 1.4	2
	7	30.3 ± 1.6	7
Cortex	13	31.4 ± 2.3	0
	10	31.0 ± 2.2	6
	11	29.2 ± 2.0	10

antidepressants on LIBS seizures are presented in Fig. 1. Amitriptyline produced antagonism of kindled seizures from the amygdala at doses (10 and 20 mg/kg, IP) which did not significantly affect seizure duration in the cortex; at the highest dose tested (40 mg/kg, IP) seizures were attenuated in both the amygdala and the cortex. However, with imipramine, the lowest acute dose (20 mg/kg, IP) that significantly antagonized amygdaloid seizures also significantly attenuated cortical seizures.

Acute administration of the atypical antidepressant, iprindole, over a wide range of doses (40–160 mg/kg, IP), failed to result in a significant attenuation of amygdaloid seizures (see Fig. 1). In addition, at the highest dose tested (160 mg/kg, IP) against amygdaloid seizures, cortical seizures were likewise unaffected. Acute administration of mianserin did not significantly alter amygdaloid seizures at 10 and 30 mg/kg, IP, or cortical seizures at 30 and 100 mg/kg, IP. How-

ever, at 100 mg/kg, IP, mianserin selectively altered amygdaloid seizures (see Fig. 1).

The effects of subacute treatment with selected antidepressants on kindled seizures are presented in Fig. 2. Amitriptyline produced a significant decrease in both amygdaloid and cortical seizure duration following 2-day subacute administration at a dose (10 mg/kg, IP) which was acutely ineffective in the cortex (see Fig. 2). Likewise, 5-day administration of amitriptyline also significantly altered seizure duration in both the amygdala and the cortex.

Subacute 2-day administration of imipramine, at a dose that did not affect seizures acutely (10 mg/kg, IP), significantly antagonized seizures in both the amygdala and the cortex (see Fig. 2). Similar results were also obtained after 5-day administration.

Subacute administration of the atypical antidepressant, iprindole (80 mg/kg, IP for 2 days), did not significantly affect seizures in the amygdala. Higher subacute doses could not be tested since toxicity was observed.

Subacute 2-day administration of mianserin (30 mg/kg, IP) produced a significant reduction in seizure duration in the amygdala. Although mianserin also tended to reduce seizure duration in the cortex, statistical significance was not obtained. Thus, a dose of mianserin which did not significantly alter seizures after acute administration, produced a selective blockade of kindled seizures in the amygdala after subacute administration.

DISCUSSION

The present investigation demonstrated significant effects of the antidepressants on the limbic system, as first suggested by Horovitz [11,12]. However, it failed to reveal the typical "antidepressant profile," i.e., the selective antagonism of seizures kindled from the amygdala with little or no effect on cortical seizure duration, as described by Babington and Wedeking [2]. Whereas amitriptyline, but not imipramine, exhibited this selectivity following acute administration, neither agent exhibited the desired profile following subacute treatment with a dose that was acutely ineffective in the cortex. Thus, although our results with amitriptyline are in agreement with those of Babington and Wedeking [2], we could not replicate the selective antagonism of amygdaloid seizures previously reported by them with imipramine. In addition, the magnitude of effect of both 2-day and 5-day subacute treatment vs acute administration of either tricyclic antidepressant on amygdaloid and cortical kindling remained essentially the same. Babington [3] examined the effects of chronic administration of an acutely ineffective dose of amitriptyline and reported a significant reduction in seizure duration after 14 days; he did not, however, investigate the effects of the drug on cortical seizure duration.

Although Babington [3,4] found mianserin, a clinically effective antidepressant, to be inactive in the kindling model, the present data indicate that mianserin selectively attenuated kindled seizures from the amygdala following both acute and subacute administration. Similarly, Ashton and coworkers [1] reported that mianserin significantly attenuated the duration of forepaw clonus in amygdaloid kindled rats. In agreement with Babington [3,4], iprindole failed to significantly alter seizures kindled from either site.

The failure to observe any significant selectivity of the antidepressants for one site over the other following both acute and subacute administration and the contrasting data obtained from the present experiments might be explained, in part, by the variations in the kindling process within different strains of the same species [6]. Stach and coworkers [16] investigated the effects of both the typical antidepressants, such as mianserin, on various parameters of the kindling phenomenon in the rabbit. They found that whereas imipramine inhibited all parameters of amygdaloid kindled seizures, mianserin decreased significantly only the intensity, but not the duration of behavioral seizures. They concluded that due to the diverse effects of the clinically effective antidepressants tested, kindling is not a good pharmacological model to detect new types of antidepressive agents. This conclusion is consistent with that of Ossowska and Wolfarth [14] who attributed the antiseizure activity exhibited by drugs such as imipramine and mianserin to their anticonvulsant properties rather than their antidepressant properties.

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