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Dose-Dependant Proconvulsant and Anticonvulsant Actions of the Alpha$_2$ Adrenergic Agonist, Xylazine, on Kindled Seizures in the Rat

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JOY, R. M., L. G. STARK AND T. E. ALBERTSON. *Dose-dependant proconvulsant and anticonvulsant actions of the alpha$_2$ adrenergic agonist, xylazine, on kindled seizures in the rat.* PHARMACOL BIOCHEM BEHAV **19**(2) 345–350, 1983.—The effects of the alpha$_2$ adrenergic agonist, xylazine, was evaluated on kindling acquisition and on kindled seizure expression in rats. Dose-dependant proconvulsant and anticonvulsant properties were found. The proconvulsant effects were observed at low (0.3 mg/kg) doses. In previously kindled rats these consisted of a decrease in afterdischarge threshold and an increase in the length and severity of the accompanying seizure. This dose also facilitated the rate of kindling in naive subjects. The anticonvulsant effects were observed at higher dose levels (3–20 mg/kg) which also produced sedation and ataxia. If these effects upon kindling are related to the adrenergic actions of xylazine, then it is proposed that the proconvulsant effects are associated with alpha$_2$ receptor activation and the anticonvulsant effects with alpha$_1$ receptor activation.

Adrenergic drugs Adrenergic agonists Alpha$_2$ adrenergic agonists Amygdala Seizures Nervous system Kindling Experimental epilepsy

MANIPULATIONS which affect the level of adrenergic activity in the central nervous system (CNS) commonly affect seizure susceptibility or severity. This phenomenon has been observed in a number of different animal models of epilepsy. For example, destruction of catecholaminergic neurons by intraventricular injection of 6-hydroxydopamine markedly potentiates convulsions produced by pentylenetetrazol [7, 8, 26, 29]. Similar pretreatment can also facilitate the acquisition and expression of kindled seizures [1, 7, 9]. Although 6-hydroxydopamine destroys dopaminergic and adrenergic neurons, more selective approaches have implicated the destruction of adrenergic neurons as the significant event [9, 26, 28].

The kindled amygdaloid seizure (KAS) model has been particularly helpful in uncovering the role of the adrenergic system in the control of seizures [6, 27, 32]. In addition to the effects of 6-hydroxydopamine already described, depletion of catecholamines with reserpine [1,43] or tetrabenazine [43] enhances seizure responses during kindling. Similar enhancement has been described after treatment with alpha-methyl-para-tyrosine or disulfiram [4] both of which reduce the synthesis of norepinephrine. Ehlers, Clifton and Sawyer [14] have reported that bilateral knife cuts in the mesencephalon at a level through which noradrenergic neurons pass also result in a significant facilitation of kindling. They observed a positive correlation between the number of afterdischarges (ADs) required to kindle their subjects and the concentration of norepinephrine present in the amygdala and surrounding regions. Conversely, treatment with pargyline, a monoamine oxidase inhibitor, which increases norepinephrine levels, reduced AD durations during kindling and retarded the rate of acquisition [43]. These studies suggest that activation of adrenergic systems may act to suppress seizure onset, generalization and duration. A reduction in adrenergic function would tend to decrease seizure threshold, facilitate generalization and, in certain situations, lead to longer and more severe seizures.

The role of specific adrenergic receptors in this process is less clear. The studies that have been performed are often contradictory and have employed widely differing doses of adrenergic agonists and antagonists. Propranolol, a nonspecific beta adrenergic antagonist, has been reported to either facilitate [4] or have no effect [33] upon kindling acquisition. Ashton, Leysen and Wauquier [2] found proprano-

lol reduces the duration of forepaw clonus in fully kindled subjects. The alpha adrenergic antagonist, phenoxybenzamine, has no important effects upon kindling acquisition [4] or on kindled seizures [2]. The alpha adrenergic agonist, clonidine, has been reported to have no effect on kindling acquisition [4]. It does, however, exhibit anticonvulsant properties in kindled subjects [2]. Clearly, no coherent picture of receptor-mediated action is possible from these studies.

In view of the biphasic nature of the dose-response curves that have been reported for alpha agonists such as clonidine in other model systems of epilepsy [24, 30, 31], a comprehensive dose-response study of adrenergic agonists and antagonists on different phases of the kindling process was needed. In this paper we present dose-response data for a relatively specific $alpha_2$ receptor agonist, xylazine. Like clonidine, xylazine activates both $alpha_1$ and $alpha_2$ receptors, but it is a more specific agonist for $alpha_2$ receptors than clonidine [11]. Xylazine is also widely used in veterinary medicine for its sedative and analgesic actions, both of which have been attributed to its selective $alpha_2$-adrenergic activity [10, 13, 17, 36, 37]. The results demonstrate that xylazine possesses significant proconvulsant and anticonvulsant potential. The effect produced in any particular situation is dependent upon dose.

METHOD

Subjects

Male Sprague-Dawley rats, weighing from 300–325 g, were the subjects. They were housed individually with free access to food and water. A 7 a.m. to 7 p.m. light-dark cycle was maintained.

Preparation of Subjects for Amygdaloid Stimulation

All subjects were anesthetized with Chloropent® (3.6 ml/kg) (a chloral hydrate, pentobarbital, magnesium sulfate mixture) IP. The skull was exposed and holes were drilled with a dental burr to place electrodes. An electrode consisting of a pair of 34 ga stainless steel wires, twisted tightly together and insulated except at the tips, was lowered into the right amygdala using the coordinates: 1.0 mm posterior to bregma, 4.75 mm lateral of the midline and 7.5 mm ventral from the surface of the brain (stereotaxic orientation — incisor bar 5 mm above intra-aural line). Stainless steel screws were placed over the cortex and the frontal sinus to serve as recording and reference electrodes, respectively. Additional screws were placed to anchor the final electrode assembly to the skull. The amygdala, a cortical and reference electrodes were connected by insulated wires to male Amphenol connector pins and inserted into a male Amphenol connector strip. This assembly was attached to the skull with dental acrylic cement. Animals were allowed at least 10 days to recover from the surgical procedures before being used in any of the experiments.

Procedures Used to Produce Amygdaloid Kindling

For each kindling trial subjects were placed in a Plexiglas box, 30×30×45 cm in size. The electrodes were connected via a central cable to the stimulating and recording equipment. Electrical stimulation was produced by a Grass S-44 stimulator and delivered to the amygdala through a constant current output. The stimulus consisted of a one second train of 60 Hz biphasic square waves, each 1 msec in duration and 400 μAmp in amplitude. At the termination of the stimulus train, the amygdala and the EEG electrodes were electronically switched to a Grass Model 7 polygraph. Electrical activity from the amygdala and the cortex was recorded until all evidence of seizure activity had ceased.

Two measurements of seizure severity were employed. The first was the duration of AD elicited by the stimulus. The AD was the period during which electrographic spiking at a frequency of 1 per second or faster and at least twice the maximal prestimulus amplitude, was recordable in amygdala and/or cortex. If additional AD occurred within 1 minute of the termination of the preceding AD, it was included when determining total AD duration. The second measure employed was an assessment of behavioral seizure severity. A ranking scale, similar to that described by Racine [34] was used in which a score of (0) was assigned for no behavioral response; (1) indicated facial clonus; (2) indicated 1 plus head nodding or head and neck clonus; (3) indicated 2 plus forelimb clonus; (4) indicated 3 plus rearing; and (5) indicated rearing and falling over onto the cage floor. Only subjects completing the full acquisition period were counted in the results. Data from animals dying, losing their implants or exhibiting abnormal ADs or behavioral responses were discarded.

Procedure Used to Determine Seizure Thresholds

In previously kindled subjects seizure thresholds were determined at 1 minute intervals with increasingly higher current intensities until an AD occurred. The initial current (20 μAmps) was increased by 20 μAmp increments. The threshold was defined to be the lowest current intensity producing an Ad. In order to be considered an AD the response to stimulation had to include at least three spikes occurring at a frequency of 1 per second or faster. The duration of the AD and the severity of the seizure produced by threshold stimulation were also measured.

Experiment 1: Xylazine and Kindled Amygdaloid Seizures (KAS)

Forty previously kindled rats were used to evaluate the effect of xylazine on KAS expression. All had been without drug exposure for at least two weeks. Their responses to amygdaloid stimulation were characterized by a stable threshold for evoking ADs and by ADs and seizures which were constant in duration and expression from trial to trial. Upon entering the study each rat was assigned randomly to one of two groups. One of these groups was used to evaluate effects upon supramaximal (400 μAmp) stimulation and the other was used to evaluate effects upon AD thresholds. The following testing schedule was used for both groups. Every week each subject was randomly assigned to one of six xylazine (Rompun-Chemagro) dose groups (0.3, 1, 3, 10, 20 or 30 mg/kg). On day 1 rats were given a suprathreshold stimulation. On day 2 rats received saline (ml/kg) or xylazine in a random order. Twenty minutes later seizure thresholds were determined or the subjects received a single 400 μAmp stimulation, depending upon group. On day 3 nothing was done. Day 4 was a repeat of day 1, and day 5 was a repeat of day 2 except subjects were crossed over so that those receiving saline on day 2 received xylazine on day 5 while subjects receiving xylazine were administered saline. This schedule was repeated weekly until all 6 treatments had been completed.

For a number of reasons, not all subjects received all doses of xylazine. The doses of 20 and 30 mg/kg produced prolonged effects which invalidated the crossover component in half the subjects receiving these doses. Because of this, doses of 20 and 30 mg/kg were not used in the threshold group. Subjects showing changes of more than 20% between successive saline trials or other evidence of unstable responses were also discontinued. Because of this fact, all analyses of xylazine effects were restricted to a within subjects comparison where the treatment effect was compared only against the saline control data obtained for the same week (e.g., day 2 vs. day 4).

Experiment 2: Xylazine and the Acquisition of Kindled Seizures

Based upon the results obtained in the experiments on kindled subjects, doses of 0.3 and 3 mg/kg were selected for a kindling acquisition study. These doses were anticipated to produce opposite effects on kindling acquisition. Ten days after surgery, rats were given daily intraperitoneal injections of saline (ml/kg) (N=6), 0.3 mg/kg xylazine (N=7) or 3 mg/kg xylazine (N=6). Electrical stimulation of the amygdala (400 μAmp) was given 20 minutes later. Each rat was injected and stimulated daily for 16 days, at which time all subjects had kindled. Kindling was defined to have occurred when subjects attained their first rank=5 seizure.

Assessment of Effects

In previously kindled rats, comparisons of AD threshold and AD durations were performed using a paired-sample t-test. Seizure severity ranks were compared with Wilcoxin's paired-sample signed ranks test. Behavioral indices were evaluated using a simple three point scale. Rats that were immobile, exhibited decreased muscle tone or didn't respond to handling were scored as sedated. Rats showing disturbance of gait were scored as ataxic. Rats showing an attenuated response or failing to respond to a calibrated tail pinch were scored as analgesic.

The kindling data in Experiment 2 were analyzed as follows. A repeated measures analysis of variance was used to compare AD durations during the acquisition period. A signed-ranks test [16] was used to compare AD seizure severity ranks. All other data were analyzed by analysis of variance. Intergroup differences between means were determined using the revised method of least significant differences [39].

RESULTS

Kindled Subjects—Suprathreshold Stimulation

The effects of xylazine upon KAS expression in kindled subjects were determined over a dose range from 0.3–30 mg/kg (Table 1). Seizures evoked with suprathreshold stimulation were relatively resistant to modification by the alpha$_2$/alpha$_1$ agonist. Seizure duration and severity were affected only at doses that also produced sedation, analgesia and ataxia. Rats that received 20 or 30 mg/kg xylazine exhibited toxicity that lasted 2–4 days. This consisted of weight loss, diarrhea and an unkept appearance. Four subjects given 30 mg/kg died 12–24 hours after exposure. Autopsy revealed extensive pulmonary edema and hemorrhage, possibly attributable to alpha$_1$ adrenergic activity at these dose levels. Because of these effects, doses above 10 mg/kg were not tested in the threshold group.

TABLE 1

EFFECTS OF XYLAZINE ON AMYGDALOID SEIZURE EXPRESSION IN KINDLED RATS (SUPRATHRESHOLD STIMULATION)

Dose (mg/kg)	N	Afterdischarge Duration* (% of control)	Change in Seizure Severity† (No. rank score)
0.3	10	98 ± 4‡	0.0
1	19	93 ± 6	0.0
3	20	101 ± 10	0.0
10	20	83 ± 9	−0.6
20	8	82 ± 6§	−1.6§
30	8	45 ± 5¶	−2.7¶

*Length of AD on drug day expressed as a percent of AD duration on the day subjects received saline only.

†Difference in mean seizure severity rank score from score for day subjects received saline only.

‡Values are means ± S.E.

§$p<0.05$.

¶$p<0.01$.

Kindled Subjects—Threshold Stimulation

The effects of xylazine on threshold seizures were biphasic and dose-dependent (Table 2). A dose of 0.3 mg/kg was proconvulsant. It lowered the threshold current required to elicit AD, and it markedly increased the duration of the AD and the severity of the accompanying seizure produced by the threshold stimulus. At this dose of xylazine, AD duration and seizure severity nearly equalled those produced in the same subjects by suprathreshold stimulation. At the proconvulsant dose of 0.3 mg/kg, no observable sedation, analgesia, ataxia or other change in behavior was noted.

Increasing the dose of xylazine led to a progressive replacement of this effect with an anticonvulsant one. At doses of 3–10 mg/kg seizure thresholds were elevated, and AD durations and severity were decreased. The anticonvulsant action was apparent only with doses that were also sedative and ataxic.

Kindling Acquisition

The acquisition data are shown in Fig. 1. The figure indicates the effects observed on three measures: (1) time of appearance of first fully generalized (rank=5) seizure, (2) mean seizure severity rank for each trial during acquisition, and (3) mean AD duration for each trial during acquisition. The group given 0.3 mg/kg day xylazine kindled faster and had more severe seizures during the acquisition period than did the controls. Conversely, the group given 3 mg/kg xylazine required more stimulations to kindle than the control group. They also had less severe seizures during the acquisition period. An important finding is that both doses of xylazine decreased AD duration during acquisition as compared to control, $F(2,16)=3.49$, $p<0.05$, yet the lower dose facilitated and the higher dose depressed acquisition rate.

Additional acquisition data are presented in Table 3. The two dose groups differed from each other and from the control group in the number of stimulations required to complete kindling. The 0.3 mg/kg group also differed from the control group and the 3 mg/kg group by requiring only 50% as much

TABLE 2

EFFECTS OF XYLAZINE ON AMYGDALOID SEIZURE EXPRESSION IN KINDLED RATS (THRESHOLD STIMULATION)

Dose (mg/kg)	N	Afterdischarge Threshold* (% of control)	Afterdischarge Duration† (% of control)	Change in Seizure Severity‡ (No. rank score)
0.3	10	83 ± 6¶	283 ± 49¶	+2.1¶
1	12	100 ± 14	144 ± 25	+0.5
3	10	123 ± 17	63 ± 22	−0.3
10	12	136 ± 21	63 ± 18§	−0.9§

*Stimulus current required to evoke an AD on drug day expressed as a percent of stimulus current required on the day subjects received only saline.

†Length of AD on drug day expressed as a percent of AD duration on the day subjects received saline only.

‡Difference in mean seizure severity rank score from score for day subjects received saline only.

§$p<0.05$.

¶$p<0.01$.

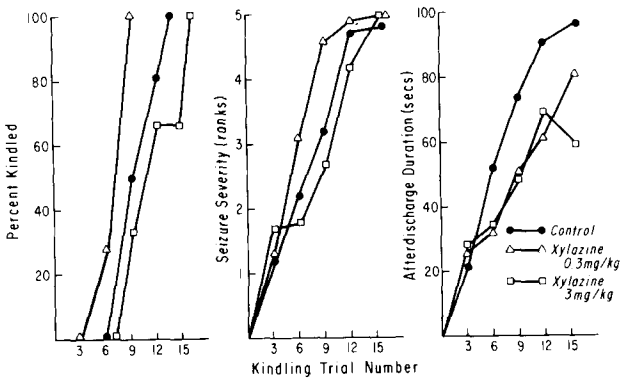

FIG. 1. Effects of xylazine on acquisition of kindling: The results of exposure to 0.3 and 3 mg/kg/day xylazine on three different acquisition measures are shown. Left—Cumulative percent of subjects having had at least one rank=5 seizure is plotted as a function of the number of kindling trials; Middle—Mean seizure severity during acquisition; Right—Mean afterdischarge duration during acquisition.

AD to complete kindling. Although the groups differed significantly in measures made during acquisition, the groups could not be differentiated from each other once kindled. The duration and severity of the kindled seizure was not modified by either treatment.

DISCUSSION

The results indicate that xylazine can have proconvulsant or anticonvulsant effects, depending upon dose. The proconvulsant effects stem from mechanisms which act to decrease AD thresholds and which may facilitate the spread of convulsive activity throughout the CNS. The former can be demonstrated directly in previously kindled subjects. The latter can be inferred from the fact that: (1) 0.3 mg/kg xylazine increased kindling acquisition rate even though it decreased AD durations on every acquisition trial, (2) subjects given 0.3 mg/kg xylazine kindled with only half the total AD exposure needed by control subjects, and (3) 0.3 mg/kg xylazine increased the duration and severity of threshold-elicited seizures in previously kindled subjects. These sei-

TABLE 3

EFFECTS OF XYLAZINE ON THE ACQUISITION OF AMYGDALOID KINDLED SEIZURES

Dose (mg/kg)	N	No. of Stimulations Required to Kindle*	Cumulative seconds of AD Required to Kindle† (sec)	AD Duration of First Kindled Seizure‡ (sec)
0	6	9.8 ± 1.0§	318 ± 79	73.8 ± 13.9
0.3	7	7.7 ± 0.8¶**	163 ± 31¶**	62.9 ± 13.7
3	6	11.8 ± 1.4¶	355 ± 41	50.7 ± 8.9
		F(2,16)=3.82	F(2,16)=3.93	F(2,16)=0.80
		L.S.D.=2.0††	L.S.D.=118	

*Number of stimulations required to elicit first fully generalized (rank=5) seizure.

†Total seconds of AD experience prior to developing first fully generalized seizure.

‡Duration of first fully generalized seizure AD.

§Values are means ± S.E.

¶$p<0.05$ As compared to the saline (0 mg/kg) control group.

**$p<0.01$ As compared to the 3 mg/kg xylazine group.

††L.S.D. is the least significant difference between means, $p<0.05$.

zures approached, but never became longer or more severe than, seizures elicited in the same subjects by supramaximal stimulation. These observations are consistent with the previous demonstration by Racine [34] that AD spread is the main electrographic correlate of kindling.

The anticonvulsant actions appear relatively nonspecific and may simply be the result of the reduction in AD length produced by xylazine. At 3 mg/kg doses or higher, AD durations and intensities were reduced in all three situations examined. Kindling acquisition was slowed, but only in proportion to the reduction in AD length. The 3 mg/kg group required more trials to become kindled than did the control group, but each AD evoked during acquisition was shorter. When total AD experience is compared, the 3 mg/kg xylazine group and the control group kindled after receiving the same amount.

These findings reinforce previous assumptions about the sensitivity of the KAS model of epilepsy [18, 19, 20, 32]. The kindling acquisition period is sensitive to manipulation by both proconvulsant and anticonvulsant influences. In fully kindled subjects threshold seizures are also responsive to both proconvulsant and anticonvulsant manipulations. Suprathreshold-elicited seizures are more resistant to manipulation and are not as suitable for the demonstration of proconvulsant effects.

Although many chemicals have been demonstrated to affect kindling, xylazine has a unique spectrum of action. It is the only substance tested to date that can facilitate kindling acquisition rate while simultaneously decreasing AD duration. Other compounds known to facilitate acquisition rate, such as lindane [18,19], dieldrin [20] or pentylenetetrazol [3] also increase AD durations throughout the acquisition period. For the latter type of proconvulsants, the major mechanism is AD prolongation. There is no decrease in the total AD experience needed to complete kindling [3, 19, 20, 33]. Xylazine, on the other hand, significantly reduces the AD requirement at proconvulsant doses and produces kindled subjects in half the exposure. This has important implications for the mechanisms by which kindling occurs.

Although these experiments do not provide direct insight into the mechanisms involved, it is worth considering how they might relate to the adrenergic actions of xylazine. One possibility is that the proconvulsant effects are associated with alpha$_2$ receptor activation whereas the anticonvulsant effects are associated with alpha$_1$ receptor activation.

Certain evidence supports this hypothesis. First, xylazine, like other alpha$_2$/alpha$_1$ agonists activates both receptor types [11, 12, 22, 23, 42]. However, it is a more potent agonist for alpha$_2$ receptors than for alpha$_1$ receptors, and it appears to be 3–4 times more selective as an alpha$_2$ agonist than clonidine [11,12]. Thus, at the low end of the dose-response spectrum, xylazine would be expected to produce a relatively pure alpha$_2$ action, whereas at higher doses a mixture of alpha$_2$ and alpha$_1$ effects would occur.

Stimulation of alpha$_2$ receptors is associated with many actions indicative of a reduction in adrenergic tone. For example, alpha$_2$ receptor stimulation has been implicated to decrease the stimulation-induced release of norepinephrine from central [12, 22, 23, 40, 42] and peripheral [11, 22, 23, 25, 42] neurons. Xylazine has been shown to reduce sympathetic tone by both a central and a peripheral action [38]. The noradrenergic neurons of the locus coeruleus possess alpha-adrenergic receptors in the vicinity of their cell bodies. These receptors appear to be alpha$_2$ receptors in type, and their activation leads to an inhibition of neuronal discharge [5]. Since the locus coeruleus is the site of origin for the majority of noradrenergic fibers, the direct activation of the somatic alpha$_2$ receptors by xylazine would lead to a global decrease in noradrenergic neuronal activity. Many of the behavioral effects of xylazine, including sedation [10, 13, 17], and analgesia [36,37] also appear to be mediated by alpha$_2$ receptors.

In the kindling model of epilepsy, other situations which decrease the level of adrenergic activity have been demonstrated to decrease seizure threshold and/or to increase the rate and extent of spread of seizure activity throughout the CNS [1, 4, 6, 7, 9, 27, 43]. If the proconvulsant actions of xylazine are adrenergically mediated, then it would seem most likely to be related to alpha$_2$ receptor stimulation and the consequential reduction in adrenergic activity. The proconvulsant effects appear at low doses where relatively selective alpha$_2$ effects should occur. The anticonvulsant effects are observed with higher doses where both alpha$_2$ and alpha$_1$ effects should overlap. It is pertinent here that King and Burham [21] have reported that the alpha$_2$ antagonists, yohimbine and piperoxan, produce biphasic responses on flash evoked afterdischarges (FEAD) in rats. Low doses decrease the amount of FEAD while higher doses return the amount to baseline.

While this hypothesis is attractive, there are observations that are difficult to reconcile with it. The sedative and analgesic properties of xylazine appear to be alpha$_2$-mediated [17, 36, 37]. These effects appear over a wide dose range and are present at doses of xylazine that are anticonvulsant. Clonidine, which is pharmacologically similar to xylazine, has been reported to have proconvulsant [29] and anticonvulsant activity [30,31] on pentylenetetrazol-induced seizures. The anticonvulsant effects occurred to low exposure levels and were antagonized by yohimbine, an alpha$_2$ antagonist. High doses of clonidine (1–5 mg/kg) are anticonvulsant against picrotoxin, strychnine and maximal electroshock seizures [24].

It is also possible that the proconvulsant and/or anticonvulsant effects of xylazine do not involve noradrenergic interactions at all. Clonidine, which is pharmacologically similar to xylazine, also activates histamine receptors in the CNS [15,35]. Clonidine has also been demonstrated to interfere with the stimulation-induced release of serotonin from serotonergic neurons [40] and to diminish acetylcholine release from nerves in the guinea pig ileum [41]. If xylazine shares any of these properties, then its mechanisms may be quite complex. However, because of the uniqueness of its actions upon kindling and kindled seizures, further analysis is clearly warranted.

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REFERENCES

1. Arnold, P. S., R. J. Racine and R. A. Wise. Effects of atropine, reserpine, 6-hydroxydopamine and handling on seizure development in the rat. *Exp Neurol* **40:** 457–470, 1973.
2. Ashton, D., J. E. Leysen and A. Wauquier. Neurotransmitters and receptor binding in amygdaloid kindled rats: serotonergic and noradrenergic modulatory effects. *Life Sci* **27:** 1547–1556, 1980.
3. Bowyer, J. F. and T. E. Albertson. The effects of pentylenetetrazol, bicuculline and strychnine on the development of kindled seizures. *Neuropharmacology* **21:** 985–990, 1982.
4. Callaghan, D. A. and W. S. Schwark. Involvement of catecholamines in kindled amygdaloid convulsions in the rat. *Neuropharmacology* **18:** 541–545, 1979.
5. Cedarbaum, J. M. and G. K. Aghajanian. Catecholamine receptors on locus coeruleus neurons: pharmacological characterization. *Eur J Pharmacol* **44:** 375–385, 1977.
6. Corcoran, M. E. Catecholamines and kindling. In: *Kindling 2*, edited by J. A. Wada. New York: Raven Press, 1981, pp. 87–101.
7. Corcoran, M. E., H. C. Fibiger, J. A. McCaughran and J. A. Wada. Potentiation of amygdaloid kindling and Metrazol-induced seizures by 6-hydroxydopamine in rats. *Exp Neurol* **45:** 118–133, 1974.
8. Corcoran, M. E., H. C. Fibiger, E. G. McGeer and J. A. Wada. Potentiation of Leptazol seizures by 6-hydroxydopamine. *J Pharm Pharmacol* **25:** 497–499, 1973.
9. Corcoran, M. E. and S. T. Mason. Role of forebrain catecholamines in amygdaloid kindling. *Brain Res* **190:** 473–484, 1980.
10. Delbarre, B. and H. Schmitt. Sedative effects of α-sympathomimetic drugs and their antagonism by adrenergic and cholinergic blocking drugs. *Eur J Pharmacol* **13:** 356–363, 1971.
11. Drew, G. M. Effects of α-adrenoceptor agonists and antagonists on pre- and postsynaptically located α-adrenoceptors. *Eur J Pharmacol* **36:** 313–320, 1976.
12. Drew, G. M. Presynaptic α-adrenoceptors: their pharmacological characterisation and functional significance. In: *Advances in the Biosciences, vol 18 Presynaptic Receptors*, edited by S. A. Langer, K. Starke and M. L. Dubocovich. New York: Pergamon Press, 1979, pp. 59–65.
13. Drew, G. M., A. J. Gower and A. S. Marriott. α_2-Adrenoceptors mediate clonidine-induced sedation in the rat. *Br J Pharmacol* **67:** 133–141, 1979.
14. Ehlers, C. L., D. K. Clifton and C. H. Sawyer. Facilitation of amygdaloid kindling in the rat by transecting ascending noradrenergic pathways. *Brain Res* **189:** 274–278, 1980.
15. Finch, L., C. A. Harvey, P. E. Hicks and D. A. A. Owen. Clonidine-induced hypotension: further evidence for a central interaction with histamine H_2 receptor antagonists in the rat. *Neuropharmacology* **17:** 307–313, 1978.
16. Goldstein, A. *Biostatistics*. New York: MacMillan Co., 1964, pp. 62–63.
17. Hsu, W. H. Xylazine-induced depression and its antagonism by alpha adrenergic blocking agents. *J Pharmacol Exp Ther* **218:** 188–192, 1981.
18. Joy, R. M., L. G. Stark and T. E. Albertson. Proconvulsant effects of lindane: Enhancement of amygdaloid kindling in the rat. *Neurobehav Toxicol Teratol* **4:** 347–354, 1982.
19. Joy, R. M., L. G. Stark and T. E. Albertson. Proconvulsant actions of lindane: Effects on afterdischarge thresholds and durations during amygdaloid kindling in rats. *Neurotoxicology*, in press, 1983.
20. Joy, R. M., L. G. Stark, S. L. Peterson, J. F. Bowyer and T. E. Albertson. The kindled seizure: Production of and modification by dieldrin in rats. *Neurobehav Toxicol* **2:** 117–124, 1980.
21. King, G. A. and W. M. Burnham. α_2-Adrenergic antagonists suppress epileptiform EEG activity in a petit mal seizure model. *Life Sci* **30:** 293–298, 1982.
22. Kobinger, W. and L. Pichler. Relation between central sympathoinhibitory and peripheral pre- and postsynaptic α-adrenoceptors as evaluated by different clonidine-like substances in rats. *Naunyn Schmiedebergs Arch Pharmacol* **315:** 21–27, 1980.
23. Kobinger, W. and L. Pichler. Investigation into different types of post- and presynaptic α-adrenoceptors at cardiovascular sites in rats. *Eur J Pharmacol* **65:** 393–402, 1980.
24. Kulkarni, S. K. Actions of clonidine on convulsions and behaviour. *Arch Int Pharmacodyn* **252:** 124–132, 1981.
25. Langer, S. Z. Presynaptic receptors and their role in the regulation of transmitter release. *Br J Pharmacol* **60:** 481–497, 1977.
26. Mason, S. T. and M. E. Corcoran. Catecholamines and convulsions. *Brain Res* **170:** 497–507, 1979.
27. McIntyre, D. C. Catecholamine involvement in amygdala kindling of the rat. In: *Kindling 2*, edited by J. A. Wada. New York: Raven Press, 1981, pp. 67–80.
28. McIntyre, D. C., M. Saari and B. A. Pappas. Potentiation of amygdaloid kindling in adult or infant rats by injection of 6-hydroxydopamine. *Exp Neurol* **63:** 527–544, 1979.
29. Oishi, R., N. Suenaga, T. Hidaka and T. Fukuda. The role of α-adrenoceptors in the regulation of pentylenetetrazol convulsions in mice. *J Pharm Pharmacol* **31:** 709–710, 1979.
30. Papanicolaou, J., R. J. Summers, R. J. E. Vajda and W. J. Louis. Anticonvulsant effects of clonidine mediated through central α_2-adrenoceptors. *Eur J Pharmacol* **77:** 163–166, 1982.
31. Papanicolaou, J., R. J. Summers, F. J. E. Vajda and W. J. Louis. The relationship between α_2-adrenoceptor selectivity and anticonvulsant effect in a series of clonidine-like drugs. *Brain Res* **241:** 393–397, 1982.
32. Peterson, S. L. and T. E. Albertson. Neurotransmitter and neuromodulator function in the kindled seizure and state. *Prog Neurobiol* **19:** 237–280, 1982.
33. Peterson, S. L., T. E. Albertson, L. G. Stark, R. M. Joy and L. S. Gordon. Cumulative after-discharge as the principal factor in the acquisition of kindled seizures. *Electroencephalogr Clin Neurophysiol* **51:** 192–200, 1981.
34. Racine, R. J. Modification of seizure activity by electrical stimulation: II. motor seizure. *Electroencephalogr Clin Neurophysiol* **32:** 281–294, 1972.
35. Sastry, B. S. R. and J. W. Phillis. Evidence that clonidine can activate histamine H_2-receptors in rat cerebral cortex. *Neuropharmacology* **16:** 223–225, 1977.
36. Schmitt, H., J.-C. Le Douarec and N. Petillot. Antinociceptive effects of some α-sympathomimetic agents. *Neuropharmacology* **13:** 289–294, 1974.
37. Schmitt, H., J.-C. Le Douarec and N. Petillot. Antagonism of the antinociceptive action of xylazine, an α-sympathomimetic agent, by adrenoceptor and cholinoceptor blocking agents. *Neuropharmacology* **13:** 295–303, 1974.
38. Schmitt, H., G. Fournadjiev and H. Schmitt. Central and peripheral effects of 2-(2,6-dimethylphenylamino)-4-H-5,6-dihydro-1,3-thiazin (Bayer 1470) on the sympathetic system. *Eur J Pharmacol* **10:** 230–238, 1970.
39. Snedecor, G. W. and W. G. Cochran. *Statistical Methods*, 6th edition. Ames, Iowa: Iowa State University Press, 1967, pp. 271–275.
40. Starke, K. and H. Montel. Involvement of α-receptors in clonidine-induced inhibition of transmitter release from central monoamine neurones. *Neuropharmacology* **12:** 1073–1080, 1973.
41. Werner, U., K. Starke and H. J. Schumann. Actions of clonidine and 2-(2-methyl-6-ethyl-cyclohexylamine)-2-oxazoline on postganglionic autonomic nerves. *Arch Int Pharmacodyn Ther* **195:** 282–290, 1972.
42. Wikberg, J. E. S. Pre- and postjunctional α-receptors. In: *Advances in the Biosciences, vol 18, Presynaptic Receptors*, edited by S. A. Langer, K. Starke and M. L. Dubocovich. New York: Pergamon Press, 1979, pp. 117–123.
43. Wilkison, D. M. and L. M. Halpern. The role of biogenic amines in amygdalar kindling. I. local amygdalar afterdischarge. *J Pharmacol Exp Ther* **211:** 151–158, 1979.