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Effects of Central Administration of Kynurenic Acid on Spontaneous Locomotor Activity in the Kindled Rat: A Multivariate Approach Using the Automated Digiscan Monitoring System

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DENNISON, Z., K. P. OSSENKOPP AND D. P. CAIN. *Effects of central administration of kynurenic acid on spontaneous locomotor activity in the kindled rat: A multivariate approach using the automated Digiscan monitoring system.* PHARMACOL BIOCHEM BEHAV **43**(3) 807-814, 1992. – Changes in spontaneous motor activity in kindled hooded rats were measured following intracerebroventricular administration of three doses of kynurenic acid (65, 39, and 6.5 μg, dissolved in 3.3 μl isotonic saline). Behavior was measured in the automated Digiscan system on every third day during 13 days of drug administration to assess initial behavioral impairment and the development of tolerance. Activity data were collected beginning 5 min after drug administration for six consecutive 5-min samples. The results revealed a suppressive effect of central administration of kynurenic acid on the pattern of spontaneous locomotor activity and showed the development of behavioral tolerance. Initially, the degree of suppression was dose related, but as tolerance developed group differences were minimized. Most measures returned to predrug levels by day 13 except vertical movement, which remained suppressed in the 65-μg group throughout testing. This measure may have been more sensitive to the subtle and long-lasting motor impairments resulting from kynurenic acid.

Kynurenic acid Digiscan monitoring system Behavioral impairment Drug tolerance
Multivariate assessment Excitatory amino acid antagonist Locomotor activity Rats Kindling

ANTAGONISTS of excitatory amino acids (EAAs) have been suggested as potentially useful anticonvulsants. EAA antagonists are specific in varying degrees to the main subtypes of EAA receptors. These receptors have been divided in three general subtypes, named for the agonists that preferentially activate them; kainate preferring, quisqualate preferring, and NMDA preferring (30,31). Ongoing research is dividing the non-NMDA subtypes into more precise categorizations that more accurately reflect the action of agonists and antagonists at these receptors (1,15,27).

Use of these compounds as anticonvulsants in animal research has revealed a variety of behavioral effects that must be considered before clinical use is considered. The primary feature of these effects is discoordination, ataxia, and overall suppression of behavior. Swiss and DBA/2 mice exhibited sedation, reduced or impaired locomotor activity, and ataxia when NMDA antagonists were administered (ICV) or IP (5). Meldrum et al. (17) gave 2-amino-5-phosphonovaleric acid (APV), a potent and highly selective NMDA antagonist (30), intravenously in the baboon *Papio papio* and reported signs of sedation, including drooping eyelids and loss of muscle tone. Koek et al. (13) reported catalepsy after pigeons received APV ICV. Gilbert and Mack (10) reported that the NMDA antagonist MK-801 produced an atoxic state. Studies in our laboratory indicated that ICV administration of either APV or kynurenic acid results in ataxia and overall suppression of behavior in rats (3,6).

Kynurenic acid is an endogenous tryptophan metabolite that acts as a postsynaptic EAA receptor blocker (9). Perkins and Stone (23) reported that kynurenic acid blocked EAA

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transmission at synapses using quinolinic acid, NMDA, and quisqualic acid with no preferential antagonism. However, Ganong et al. (9) reported that at low doses kynurenic acid appeared to act preferentially on the NMDA receptor.

We have reported that both APV (3) and kynurenic acid (6) significantly retard the development of kindled seizures, an experimental model of temporal lobe epilepsy (11,25), in the rat. This article consists of a quantitative analysis of the changes in spontaneous motor activity in rats used in our previous report of the effect of kynurenic acid on amygdala kindling (6). Spontaneous activity was assessed in a multivariate fashion using the Digiscan Animal Activity Monitor.

METHOD

Subjects

Male hooded rats of the Royal Victoria strain, weighing between 250–450 g at the time of surgery, were housed individually in stainless steel cages with wire mesh bottoms. The cages were kept in racks in a colony room, which was on a 12 L : 12 D cycle, with the light on from 0800–2000 h. Food (Purina lab pellets) and water were available freely, and the colony room was maintained at 22 ± 1°C. Animals were placed on trays in groups and allowed to interact freely for periods of several hours both previous to surgery and throughout the experiment.

Apparatus

The spontaneous behavior of rats was monitored using four Digiscan Animal Activity Monitors (Omnitech Electronics Inc., Columbus, OH; model RXYZCM-16) [cf. (26)]. Each monitor consisted of a clear Plexiglas box, measuring 40 × 40 × 30.5 cm, with infrared monitoring sensors mounted every 2.54 cm along the perimeter, for a total of 16 beams per side. These were 4.5 cm above the floor. In addition, a second bank of 16 sensors on two sides were located 15 cm above the floor of the box to tabulate vertical activity. Data were collected and analyzed by a Digiscan Analyzer (Omnitech Model DCM), which in turn transmitted the data to an Apple II+ computer for storage. The Plexiglas boxes were thoroughly washed between each session to remove any odor cues.

Surgery and Drug Administration

Rats were implanted with bilateral cannulae aimed at the dorsal surface of the lateral ventricles. Bilateral electrodes aimed at the basolateral amygdala were implanted at the same time using standard stereotaxic techniques (6). Four groups of animals (HI, MED, LOW, SAL) received 65, 39, 6.5, 0 μg kynurenic acid dissolved in 3.3 μl isotonic saline, respectively. All solutions were adjusted to a pH of 7.4. The solution was infused over 10 s using a Sage infusion pump (Sage Instruments, divis. of Onon Research Inc., Cambridge, MA). The injection cannula was left in place for 30 s after infusion to allow for diffusion of the drug or saline. The drug was administered every other day, followed 40 min later by electrical stimulation in a standard kindling procedure (6). Movement data were collected between 1200 and 1500 h, under normal room light levels, in the period between drug injection and electrical stimulation, beginning 5 min after drug injection.

Measurement of Spontaneous Activity

The behavioral measures were defined as follows: horizontal activity (HA), the total beam interruptions for the lower bank of sensors; number of horizontal movements (NHM), the number of continuous-beam interruptions, with a minimum 1-s cessation separating movements; total distance traveled (TD), the number of inches travelled; average speed (AS), the average distance per given time interval; movement time (MT), the number of seconds the animal was in motion during the given time sample; and vertical activity (VA), the total number of beam interruptions for the upper bank of infrared beams.

Animals were habituated in the activity monitor for two sessions prior to experimental manipulation [cf. (19)]. Data were collected for the two habituation sessions (Hab 1 and 2), the first drug day (DD1), and every third drug day thereafter (DD4, DD7, DD10, DD13). For each test session, data were summated six times at 5-min intervals and then totaled and averaged.

Forty minutes following infusion, each animal was electrically stimulated and both convulsive behavior and length of afterdischarge (AD) recorded. The kindling procedure consisted of administering a unilateral low-intensity electrical stimulation daily. This stimulus initially evokes little or no change in behavior or electrographic activity. During the course of the process, the stimulation begins to evoke convulsive behavior and complex epileptiform electrographic activity. The process is terminated when the animal has a fully generalized convulsion (6). Following testing, animals were deeply anesthetized and perfused with formalin saline, after which brains were removed, frozen, and sectioned. The placement of electrodes and cannulae was verified (22). Following verification, there were 10 animals in the HI group, 8 in the MED, 8 in the LOW, and 10 in the SAL group.

Data Analysis

The data collected by the activity monitor were analyzed in two ways. First, to determine the overall effect of the drug and reveal the development of tolerance the pattern of behavior change across days was analyzed by collapsing the six samples per day to obtain an average 5-min sample per day (20,21). These data were then examined with a group × day design repeated-measures multivariate analysis of variance (ANOVA) for all six measurements. The group factor had four levels (HI, MED, LOW, and SAL) and the day factor had five levels (DD1, DD4, DD7, DD10, and DD13). Comparisons between all four groups on DD1 and DD13 were carried out subsequently.

Second, the pattern of behavior across samples (within days) was examined with a group × day × sample design repeated-measures ANOVA for each of four measures: HA, VA, TD, and NHM. The sample factor represented the six bins of data collected within each test session at five minute intervals, and the day factor represented the two habituation sessions plus the five drug days. Separate ANOVAs were performed for the first habituation session and selected drug days for the HA and VA variables.

RESULTS

Control Group Activity Pattern

Before examination of spontaneous activity after administration of kynurenic acid, the nature of normal movement patterns in the vehicle control group was examined.

Across days. The pattern of baseline locomotion seen over the course of the experiment was demonstrated by the data from the SAL group. There were only small fluctuations in activity rate for the duration of the study (Figs. 1A–D) and the pattern was relatively stable, indicating that changes seen in the experimental groups were attributable to drug manipulations.

Across samples. A basic pattern that was relatively consistent across measures was observed in the habituation phase. Animals showed an initial high level of activity at the first sample that declined quickly with habituation and remained relatively level for the second half of the session (Figs. 2A and 3A). The only measure that differed from this basic pattern was NHM, which did not show the typical initially high peak of activity on the first sample (not shown). This suggests that while animals spend more time in motion and travel further at the beginning of a session they do so by increasing the duration of each movement, not by increasing the number of movements.

Changes in Activity After Drug Administration

Across days. A repeated-measures multivariate analysis of variance (MANOVA) was carried out, with the four groups (group) being compared across the five drug sessions (day) on all six measures (HA, VA, NHM, TD, AS, and MT). The six 5-min data summaries collected on each test day were collapsed into one average session for the across-days analyses. The multivariate tests of these data were significant (group $\times$ days, $p < 0.012$; group, $p < 0.0001$; days, $p < 0.037$). For each of the six variables, the group main effect was significant ($p < 0.0001$), as was the days main effect ($p < 0.03$). The group $\times$ days interaction was significant for MT, NHM, and HA ($p < 0.01$).

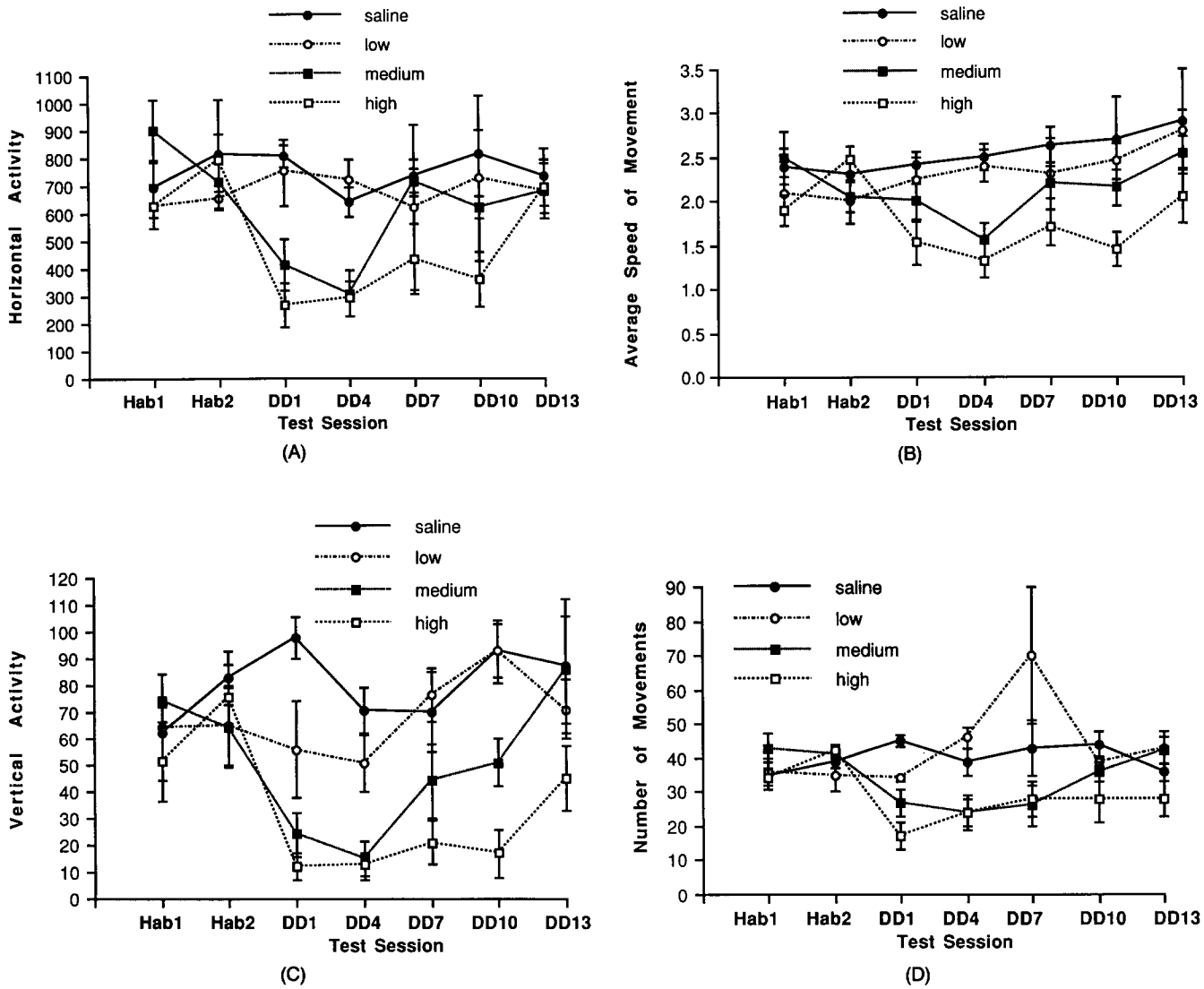

FIG. 1. Spontaneous behavior in an average 5-min sample over 2 days of habituation and 13 days of drug administration. (A) Horizontal activity. (B) Average speed. (C) Vertical activity. (D) Number of horizontal movements. Error bars are SEM.

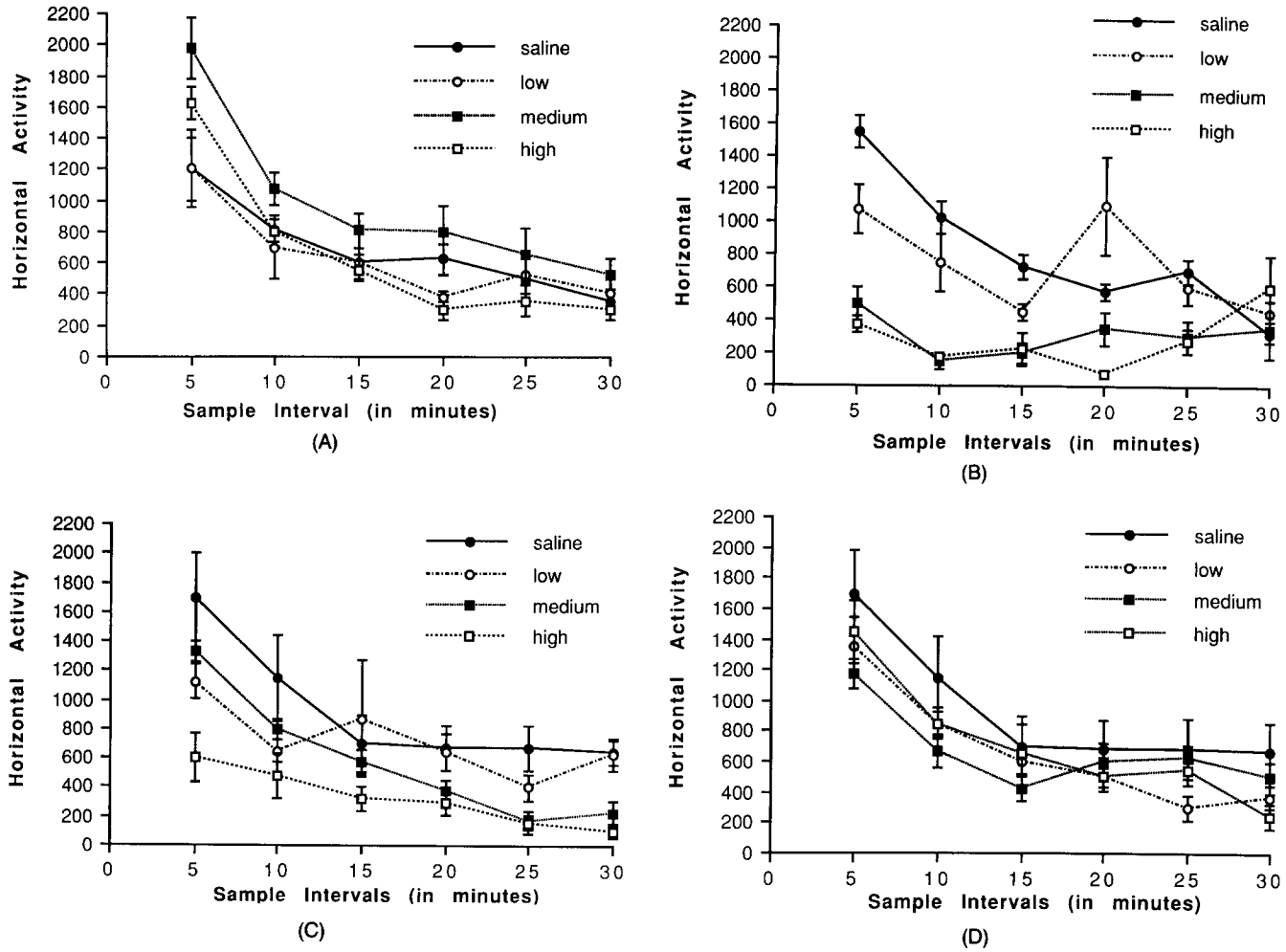

FIG. 2. Horizontal activity across samples. (A) During the first habituation session. (B) During drug day 1. (C) During drug day 10. (D) During drug day 13. Error bars are SEM.

Following the multivariate analysis, Newman-Keuls comparisons were carried out between pairs of means from the four groups on DD1 and DD13. As performance on the HA, MT, and TD measures appeared almost identical when plotted, only the statistical comparisons carried out on the HA, VA, AS, and NHM measures are discussed.

Horizontal activity. On DD1, the group effect was significant, $F(3, 32) = 8.02, p < 0.0004$. HI and MED were both significantly different from LOW and SAL ($p < 0.05$) but not from each other. LOW and SAL were not significantly different. In Fig. 1A, it can be seen that for DD1 and DD4 the HI and MED groups followed a similar pattern, as did LOW and SAL. By DD7, MED was more similar to LOW and SAL. By DD13, the group effect was no longer significant.

Average speed of movement. On DD1, the group effect was not significant ($p < 0.06$), although there was a trend for HI to be significantly different from SAL. The group factor was also not significant on DD13 ($p = 0.28$). Despite the failure of the group differences to achieve significance on DD1, visual inspection of Fig. 2B suggests some dose-related separations between the drug groups.

Vertical activity. This measure provides the best demonstration of a dose-related separation between groups (Fig. 1C). On DD1, the group effect was significant, $F(3, 32) = 12.17$, $p < 0.0001$. HI was significantly different from LOW and SAL ($p < 0.05$) but not from MED. Both MED and LOW were significantly different from SAL ($p < 0.05$). On DD13, the group effect was no longer significant but inspection of Fig. 1C suggests a weak residual dose-related drug effect.

Number of horizontal movements. On DD1, the group effect was significant, $F(3, 32) = 11.81$, $p < 0.0001$. HI, MED, and LOW were all significantly different from SAL ($p < 0.05$). HI was also significantly different from MED and LOW ($p < 0.05$). On DD13, the group effect was still significant, $F(3, 32) = 3.98, p < 0.016$. HI was significantly different from both MED and LOW ($p < 0.05$). The elevated performance of the LOW group on DD7 seems due primarily to extraordinarily high performance of two animals in this group (Fig. 1D). As this is not evident in the other measures, it means number of movements may have increased but actual time spent in movement did not.

Across samples. The pattern of motor activity was examined with a repeated-measures ANOVA for variations across samples within a test session on four measures; HA, TD, NHM, and VA. Across-day analyses were not carried out on MT and AS, as the pattern of variation over samples and days

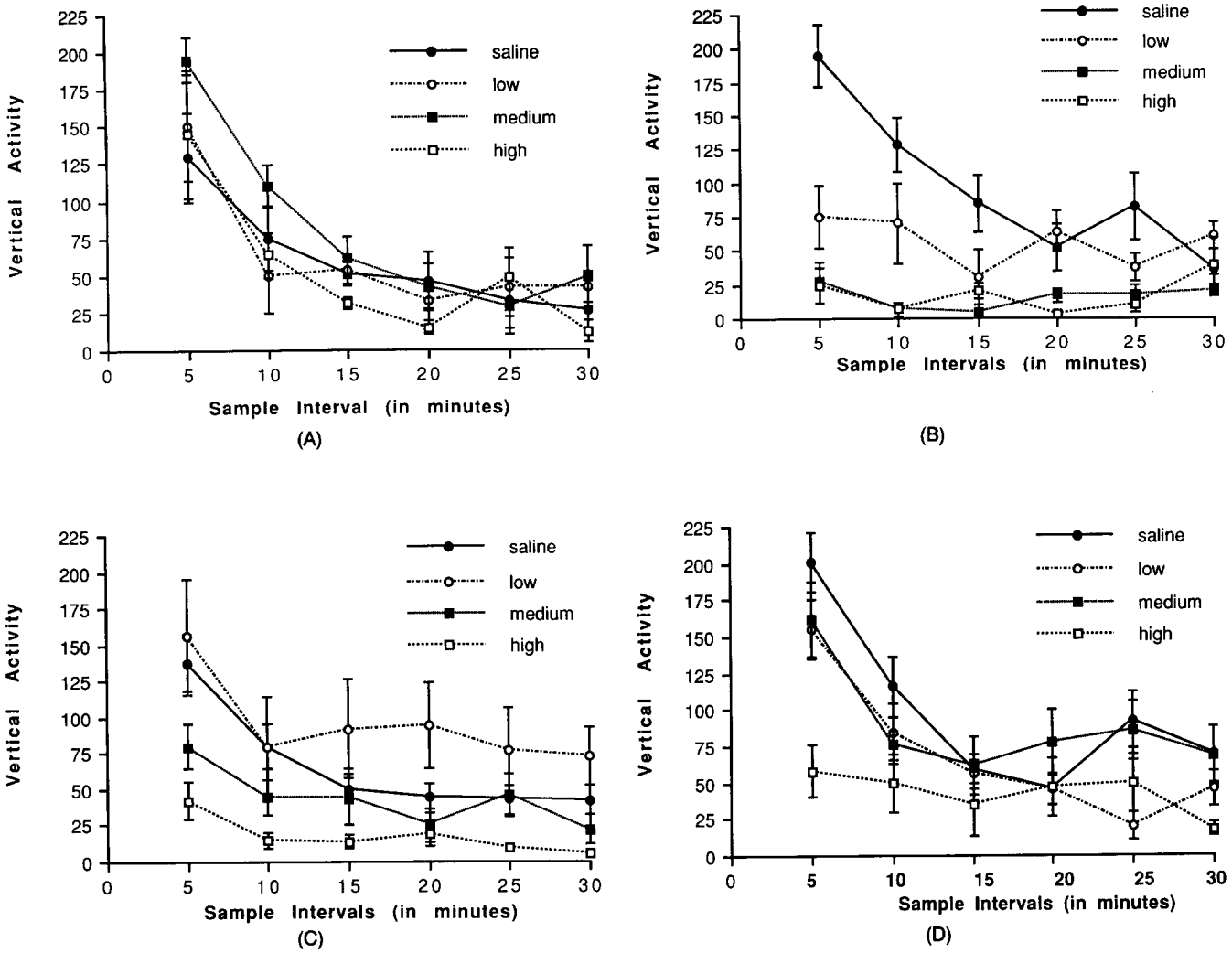

FIG. 3. Vertical activity across samples. (A) During the first habituation session. (B) During drug day 1. (C) During drug day 7. (D) During drug day 13. Error bars are SEM.

appeared identical for MT and HA and for AS and NHM when these measures were plotted. Further analyses were carried out for HA and VA on selected days.

Horizontal activity. All three main effects were significant [group, $F(3, 31) = 3.46$, $p < 0.028$; day, $F(6, 26) = 2.57$, $p < 0.043$; sample, $F(5, 27) = 54.89$, $p < 0.0001$]. Of the possible interactions, group × day, $F(18, 74.02) = 2.37$, $p < 0.005$, and group × sample, $F(15, 74.94)) = 1.95$, $p < 0.031$, were significant, but day × sample and group × day × sample were not, indicating that groups changed differentially over days and over samples. Separate ANOVAs were done on the data from each of the days shown in Fig. 2. In the first habituation session, the pattern of movement seen across samples in Fig. 2A was consistent for all groups. Groups did not differ significantly, and there was no group × sample interactions. On DD1 (Fig. 2B), groups differed significantly ($p < 0.0001$), and the group × sample interaction was significant ($p < 0.002$). On DD10 (Fig. 2C), the drug effect was reduced and the group × sample interaction was no longer significant ($p < 0.087$). By DD13 (Fig. 2D), tolerance to the effects had appeared and the original pattern seen in Fig. 2A was restored and the group × sample interaction was not significant ($p < 0.161$). The sample main effect was significant for all days ($p < 0.0001$).

Vertical activity. All three main effects were significant [group, $F(3, 31) = 6.21$, $p < 0.002$; day, $F(6, 26) = 3.12$, $p < 0.019$; sample, $F(5, 27) = 42.07$, $p < 0.0001$]. Of the possible interactions, group × day, $F(18, 74.02) = 3.13$, $p < 0.0001$, and group × sample, $F(15, 74.94)) = 1.90$, $p < 0.036$, were significant, but day × sample and group × day × sample were not. This indicates that groups differed significantly over days and over samples. Separate ANOVAs were carried out on the data from the 4 days shown in Fig. 3. The predrug pattern showed the characteristic habituation curve (Fig. 3A), and the group × sample interaction was not significant. On DD1 (Fig. 3B), groups HI and MED were completely suppressed, whereas the LOW group was halfway between the SAL group and the other two drug groups. The group × sample interaction was significant ($p < 0.0001$). By DD7 (Fig. 3C), the MED group had begun to recover and the HI group was still suppressed. Paradoxically, the group × sample interaction was not significant ($p < 0.516$) on DD7 al-

though it was significant on DD13 ($p < 0.027$). The lack of significance on DD7 may be due to the high variance and inflated performance of the LOW group. By DD13 (Fig. 3D), the MED group had reached the SAL group level but the HI group was still somewhat lower. Note that as tolerance developed the original baseline pattern of locomotor activity was reestablished with the exception of the HI group, which continued to exhibit suppression of movement. In the across-days analysis of VA, comparisons for DD13 did not show a statistical difference. The across-days analysis was based upon a daily average 5-min sample, whereas the across-samples analysis was based upon consecutive time bins. These data did reveal significant differences, as indicated by the significant group × sample interaction ($p < 0.027$) and group main effect ($p < 0.05$).

Total distance travelled. (Data are not shown.) Both the day main effect, $F(6, 26) = 4.93, p < 0.002$, and the sample main effect, $F(5, 27) = 79.68, p < 0.0001$, were significant. Group differences did not achieve significance, but a trend for differences was observed ($p < 0.10$). Of the possible interactions, the group × day, $F(18, 74.02)) = 2.91, p < 0.001$, and the group × sample, $F(15, 74.94)) = 1.96, p < 0.03$, were significant, but the day × sample and the group × day × sample were not. This indicates that groups differed significantly over days and over samples. The first habituation session showed the standard habituation pattern over the six within-day samples. The initial administration of the drug (DD1) produced a general flattening of activity for the entire session for all three drug groups, showing little dose separation. By DD7, the normal activity pattern was reestablished, but the HI group still showed reduced distance traveled. By DD13, both normal patterns and normal levels of distance were present.

Number of horizontal movements. (Data are not shown.) All three main effects were significant [group, $F(3, 31) = 40.76$, $p < 0.0001$; day, $F(6, 26) = 10.79, p < 0.0001$; sample, $F(5, 27) = 30.01, p < 0.0001$]. All possible interactions were significant [group × day, $F(18, 74.02) = 8.95, p < 0.0001$; group × sample, $F(15, 74.94) = 5.2, p < 0.0001$; day × sample, $F(2, 30) = 32.0, p < 0.031$; group × day × sample, $F(6.87, 90) = 3.69, p < 0.038$]. This measure differed from the other measures in terms of patterns across sessions and days. The characteristic within-session habituation curve was absent, and behavior declined gradually over the session in a linear fashion. Initial drug administration (DD1) resulted in suppression of number of movements in a dose-related pattern, but by DD13 tolerance had developed and the pattern more closely resembled predrug behavior.

DISCUSSION

The results indicate a suppressive effect of central administration of kynurenic acid on the pattern of spontaneous locomotor activity and show development of behavioral tolerance to this drug. This effect followed a dose–response pattern initially, and with repeated administration suppression was reduced and behavioral tolerance demonstrated as activity level increased toward predrug baseline. After 13 administrations of the drug, the HI and MED groups no longer differed from the SAL group on almost all measures. The exception was vertical movement, where the HI group remained suppressed in comparison with the SAL group. Perhaps vertical movements (rearing) required more coordination, balance, and muscular effort than any of the other movement measures and therefore may have reflected a residual loss of coordination or strength still present in the HI group upon the 13th drug administration that was not detected by the other measures. Tolerance to this effect might have developed if kynurenic acid had been administered for a longer time period. The vertical movement measure was also more sensitive in terms of dose-related separations between the various groups, showing a separation between the LOW and SAL groups that was not as apparent on other measures.

When the levels of activity within a session were examined, drug administration initially reduced levels of activity and flattened the curve that was characteristic of predrug and control group performance. As tolerance developed, this predrug pattern of movement reappeared before the level of activity reached control levels.

Interpretation of these results must take into consideration that all groups underwent kindling from DD1–DD13. The effect of the kindling process on spontaneous behavior is unclear. Behavior changes have been noted in animals that have had several fully generalized convulsions (4,7,24). These findings are not applicable in our study, as our animals did not have a fully generalized convulsion during the behavioral testing and displayed only minimal convulsive behavior during the initial behavioral testing (DD1, DD4), where the greatest impairments were seen. The data in Fig. 1 reveal that over the course of testing animals return to prekindling (Hab 1 and Hab 2) rates of activity, presumably due to the development of tolerance to the drug effects. This suggests that the changes in spontaneous behavior can be attributed primarily to the action of kynurenic acid.

The degree of tolerance seen in this study contrasts with the report by Boast et al. (2), who found only a slight tolerance to the impairments induced by CGS 19755, a competitive NMDA receptor blocker, in mice. These differences may be due to the specificity of CGS 19755 as an NMDA receptor blocker and possible species differences.

One interesting behavioral effect noted after kynurenic acid administration was rats' ability to react quickly in response to certain stimuli. While no quantitative measures were obtained, it was noticed that animals that responded in an irritable manner to handling were quite capable of making coordinated and competent aggressive movements toward the hand of the experimenter when startled. Future assessments of the motor side effects of EAA antagonists should include efforts to measure the effect of arousal on motor suppression.

The underlying physiological mechanisms responsible for the changes seen in behavior are unknown at this time. One common cause for suppression of behavior as a result of administration of a drug is sickness or malaise, which could result in decreased levels or changes in pattern of motor activity as a secondary effect. However, in the present study animals remained healthy throughout the course of the experiment. No changes were noticed in grooming or food or water intake, and animals were even observed to gnaw food pellets following kynurenic acid administration.

Paradoxically, some researchers reported increases in behavioral output following administration of an EAA antagonist. Liebman et al. (14) gave 2-amino-7-phosphonoheptanioc acid (AP7) ICV to rats and measured their behavior in the Digiscan apparatus. Samples were taken at 20-min intervals, and they noted that behavioral activation occurred for some measures after approximately 20–40 min. These differences in observed effects might have been a function of time course differences except we did not see any behavioral activation within our 30-min measurement period following drug administration. Interestingly, Boast et al. did not observe behavioral

activation in their measure of rearing behavior, and this measure showed longer-lasting impairment in our subjects. Differences might also be due to the differential actions of kynurenic acid and AP7 at EAA receptors. This lends support to the idea that different brain sites may be involved in different behavioral effects seen after drug administration.

EAA antagonists have been suggested as possibly providing new treatments for human epilepsy (16). While this suggestion has merit, based upon the similarities between kindling and human partial epilepsy (29) and the effect of EAA antagonists on kindling, there are some drawbacks to these compounds that must be resolved before clinical administration can be recommended. Greater lipophilicity is needed to allow compounds to cross the blood–brain barrier and avoid the intracerebral administration used experimentally (16). In addition, much more information about the possible motoric and other side effects of these drugs is necessary.

A possible method of circumventing the side effects seen with ICV administration of these compounds was suggested by Frenk et al. (8), who administered several kinds of EAA antagonists subdurally onto cortex. They found that this route of administration still resulted in suppression of epileptiform activity generated by strychnine, morphine, and picrotoxin, but did not produce obvious behavioral side effects. Unfortunately, no quantitative measures of behavior were taken. It is possible that a more detailed quantitative analysis of behavior, such as in an activity monitor, might reveal more subtle drug-induced changes.

A second concern is the actual effectiveness of these compounds in established epileptic conditions. While it seems clear that EAA antagonists can retard the development of seizure activity, their effect on fully kindled seizures seems to be not as strong nor as clearly demonstrated (3,6). Although we found (6) that kynurenic acid administration did retard the rate of kindling in these rats, a measure of the rate of development of epileptiform activity, it had only a weak effect on the expression of seizures in fully kindled rats (where the epileptic state was already established).

Another consideration concerning the role of EAA antagonists as anticonvulsants is whether the retardation on rate of kindling is related to the degree of motor impairment. The differing degrees of tolerance, with some motor impairment seen while kindling was progressing, suggest that distinct neuronal mechanisms are involved in the mediation of these effects. In addition, the ability of animals, as previously discussed, to move quickly in arousing situations seems to suggest that if the seizure activity had been present it would have been expressed. Alternately, the small degree of change in AD rates lends support to the idea that convulsive behavior was suppressed while electrographic AD remained unchanged. However, it should be noted that duration is only one way in which AD can be assessed, and there are other measures, such as the amplitude of AD in the contralateral hemisphere, that seem more closely connected with degree of seizure activity (28). Meldrum and Chapman (16) suggested that further receptor subtype selectivity may result in a compound that does not block the NMDA receptors involved in motor output but still acts as an anticonvulsant.

Antagonists of EAAs have also been used to demonstrate effects on learning and memory independent of the effect on behavior (18). In a recent review of this area, Keith and Rudy (12) suggested that the motor impairments produced by these compounds and their anxiolytic properties may be primarily responsible for the observed effects on learning tasks. Our results support the idea that any conclusions about the effect of EAA antagonists on learning can only be made with knowledge about the general behavioral effects of these compounds. Rats that appear unaffected or fully tolerant to the effects of administration of these antagonists may in fact be impaired on more sensitive measures, such as rearing.

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