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MK801-Induced Hyperactivity: Duration of Effects in Rats

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HARGREAVES, E. L. AND D. P. CAIN. *MK801-Induced hyperactivity: Duration of effects in rats.* PHARMACOL BIOCHEM BEHAV **51**(1) 13–19, 1995.—MK801, a noncompetitive NMDA antagonist, induces hyperactivity, the duration of which is unknown. Thus, the hyperactivity induced by three different doses of MK801 was measured for 4 h using an automated open-field system. Adult male rats were habituated to the monitors for 1 h immediately prior to data collection. Rats were then administered one of three doses (0.05 mg/kg, $n = 15$; 0.1 mg/kg, $n = 14$; 0.5 mg/kg, $n = 11$) of MK801 or equivalent volumes of saline ($n = 14$). Upon injection, individual monitors were activated, and 48 consecutive 5-min samples were collected. Results indicated that MK801 induced hyperactivity in a dose-dependent fashion, with the two lower doses being significantly different from saline controls, but not from each other. The 0.5 mg/kg dose indicated that the peak behavioral activation occurred approximately 30 min after administration. This was followed by either a slow decline or a plateau phase, dependent upon the measure examined. By approximately 3 h after administration all measures had returned to the level of saline controls.

MK801 Hyperactivity Digiscan NMDA Learning

MK801[(+)-5-methyl-10,11-dihydro-5H-dibeno(a,d)cyclohepten-5,10-imine maleate] or dizocilpine is a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist that exerts its action through binding to associated ion channels. Because of the NMDA receptor's involvement in the induction of long-term potentiation (LTP) and the acquisition of a number of hippocampally dependent tasks, and MK801's ability to readily cross the blood–brain barrier, this drug has enjoyed widespread usage in the learning and LTP literature. As such, MK801 has been used to examine disruption of synaptic transmission and LTP in the hippocampus (1,2,6,10,17) and the disruption of radial-arm maze and water-maze tasks (3,5,12, 16,19,20). However, like most NMDA antagonists, MK801 has side effects that if not adequately controlled for, may confound the observed learning deficits (11,13). One such dose-dependent side effect of MK801 is behavioral activation or hyperactivity, which a number of groups have shown using doses ranging from 0.05 mg/kg to 1.0 mg/kg (3,11,12,22–24).

Yet, these studies all measured activity in novel environments, at a set time postinjection, and for only a brief period, typically less than 30 min. Consequently, the onset and peak of the behavioral activation were not captured, nor was the duration or change over time examined. Further, the observed hyperactivity may have been exacerbated by the normal exploration of novel environments, which could have interacted with the use-dependent nature of MK801 (11,15).

However, an attempt has been made to chart the time course of MK801-induced behavioral activation, as well as detail its behavioral topography (7). Using the Digiscan system (an automated open field, based on infrared beams, Omnitech), animals treated with a single dose of 0.5 mg/kg of MK801 were followed for 120 min postinjection, using 15-min samples. Additionally, animals were habituated to the apparatus immediately prior to injection, such that basal and not exploratory activity levels were examined. Results indicated that the activity reached its peak approximately 60 min postinjection, and that at the end of the 120-min time period, many of the behavioral measures were still elevated well above the level of saline-treated controls (7). Thus, the attempt to capture the duration of the hyperactivity was unsuccessful. Further, the 15-min samples employed allowed only a coarse charting of the changes over time.

Therefore, we reexamined the duration question, and present here basal activity data from the Digiscan system collected

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over a 4-h period postinjection, at a data resolution of 5-min samples, using doses of 0.05 and 0.1 mg/kg, and the 0.5 mg/kg dose used previously (7).

METHOD

Subjects

Fifty-four adult male Long-Evans rats were used, weighing between 250–350 g. Rats were housed individually in suspended wire mesh cages, in a standard temperature-controlled colony room, on a 12 L : 12 D cycle, with the lights out at 2000 h. All animals had free access to water and food (Purina Lab chow).

Apparatus

Six Omnitech Digiscan Animal Activity Monitors (model no. RXYZCM[16]) were used. Each monitor was 40 by 40 by 30.5 cm, with a grid of infrared beams mounted horizontally every 2.54 cm, and a second tier mounted 13.5 cm above the monitor floor consisting of a single array of beams for recording vertical movement (Omnitech Electronics, Inc., Columbus, OH). The patterns of beam interruptions were recorded and analyzed by an Omnitech DCM-8 Analysis unit in 5-min samples, and then stored on the hard disk of a 286AT microcomputer. For this experiment, the following seven activity variables were analyzed.

Number of horizontal movements (NM). Each time a break in horizontal activity occurred for a period of greater than 1 s, this variable was incremented by 1, indicating the number of separate horizontal movements executed by the animal in a given sample period.

Time spent in horizontal movement (MT). As long as the animal was moving, this variable was incremented. If the animal was stationary for more than 1 s, this parameter was no longer incremented.

Number of vertical movements (VM). Each time the animal reared up and broke the second tier of infrared beams, this variable was incremented by 1. The animal was required to drop below the level of the vertical sensors for at least 1 s before the next rearing would be registered. Given sufficient lateral motion, vertical movements would also be registered by the lower horizontal grid as horizontal movements.

Time spent in vertical movement (VT). When the animal activated the vertical tier of sensors by rearing, this variable started incrementing and continued to increment until the animal went below the level of the vertical sensors.

Total distance travelled (TD). The distance travelled by the animal during the sample was measured by analyzing the pattern of interruptions on the 16 by 16 grid of infrared beams and computing the subsequent distance vectors.

Average distance travelled per movement (AD). This variable was derived from the previously computed total distance and number of movements using the formula [TD/NM] = AD.

Average speed per movement (AS). This variable was derived from the previously computed total distance and time in movement using the following formula [TD/MT] = AS.

General Procedures

Animals were tested in nine groups of six animals each. The different-dosed rats, from group to group, were distributed throughout the six monitors in a psuedorandom fashion, with each group consisting of a minimum of two different MK801 doses and at least one saline-injected control. The rats were habituated to the Digiscan apparatus by placing them in the monitors for 1 h prior to the commencement of data collection. Animals then received either 0.05 mg/kg (n = 15), 0.1 mg/kg (n = 14), 0.5 mg/kg (n = 11) of MK801, or equivalent volumes of saline (n = 14) administered intraperitoneally. Individual monitors were then activated, immediately following the injections. Forty-eight consecutive 5-min samples were collected, for a total time of 4 h. The experiment took place over 2 weeks, with each of the nine groups starting the habituation period at approximately 1200 h and the data collection starting and ending at 1300 and 1700 h, respectively.

RESULTS

The mean data from the seven activity measures for each dose were plotted across the 48 samples, of which selected measures and doses (0.05 mg/kg, 0.5 mg/kg, and saline) have been displayed in Figs. 1 and 2. Based solely on the pattern of activation of the highest dose group (0.5 mg/kg), the experiment was divided into four phases, as delineated in Figs. 1 and 2. The first phase denoted the onset and time course of the increase in activity (25 m); the second phase denoted the peak, plateau, and/or initial decline of activity (90 m); the third phase denoted the period of greatest decline (60 m); and the fourth phase denoted an apparent return to the baseline levels of the saline-treated rats (60 m). Initial multivariate analyses indicated that significant dose effects were present in all but the fourth phase, and that dose interacted with phase, such that differences between doses changed across the phases (analyses not shown). As such, univariate analyses were deemed allowable and, consequently, performed. The univariate analyses involved examining the seven measures within each phase for effects of dose (saline, 0.05 mg/kg, 0.1 mg/kg, and 0.5 mg/kg MK801) changes in these effects over time (samples), and any interactions between sample and dose. Subsequently, again within each phase, each dose of each mesaure was analyzed for linear, quadratic, and/or cubic trends across the samples. Finally, Newman-Keuls post hoc tests of means examined each of the seven measures at each of the 48 samples, for simple differences between the doses. To conserve space when multiple F-ratios of identical degrees of freedom are presented, only the lowest of the significant statistics are reported below. Thus, unless otherwise specified, the unreported F-ratios are always greater in value than those reported. Additionally, for the reported F-ratios, the associated activity measure is indicated, and where appropriate, the dose and nature of the trend are also indicated.

During the first phase, all seven measures exhibited changes in dose across the samples, $F(3, 50) > 3.048$, $p < 0.037$. However, only the nonvertical measures (TD, AD, AS, NM, MT) exhibited main effects of dose, $F(3, 50) > 9.63$, $p < 0.0005$; NM. When the trend analyses were performed on the data at individual doses, the same measures (NM, MT, TD, AD, AS) showed significant linear increases for the 0.5 mg/kg MK801 dose, $F(1, 10) > 9.708$, $p < 0.011$; AS, while the 0.05 and 0.10 mg/kg MK801 doses showed mixed patterns of either linear or quadratic changes for most measures, $F(1, 13) > 4.885$, $p < 0.046$; NM at 0.1, lin. Exceptions were the measures of AS, which showed no significant trends at either lower dose, and NM, which showed no significant trends at the 0.05 mg/kg MK801 dose, although all three showed trends towards significance, $F(1, 14) > 3.518$, $p < 0.082$; AS at 0.05. The vertical measures (VM, VT) also exhibited significant linear decreases during the first phase, $F(1, 13) > 8.401$, $p < 0.012$; VT at 0.1. These analyses show a direct and imme-

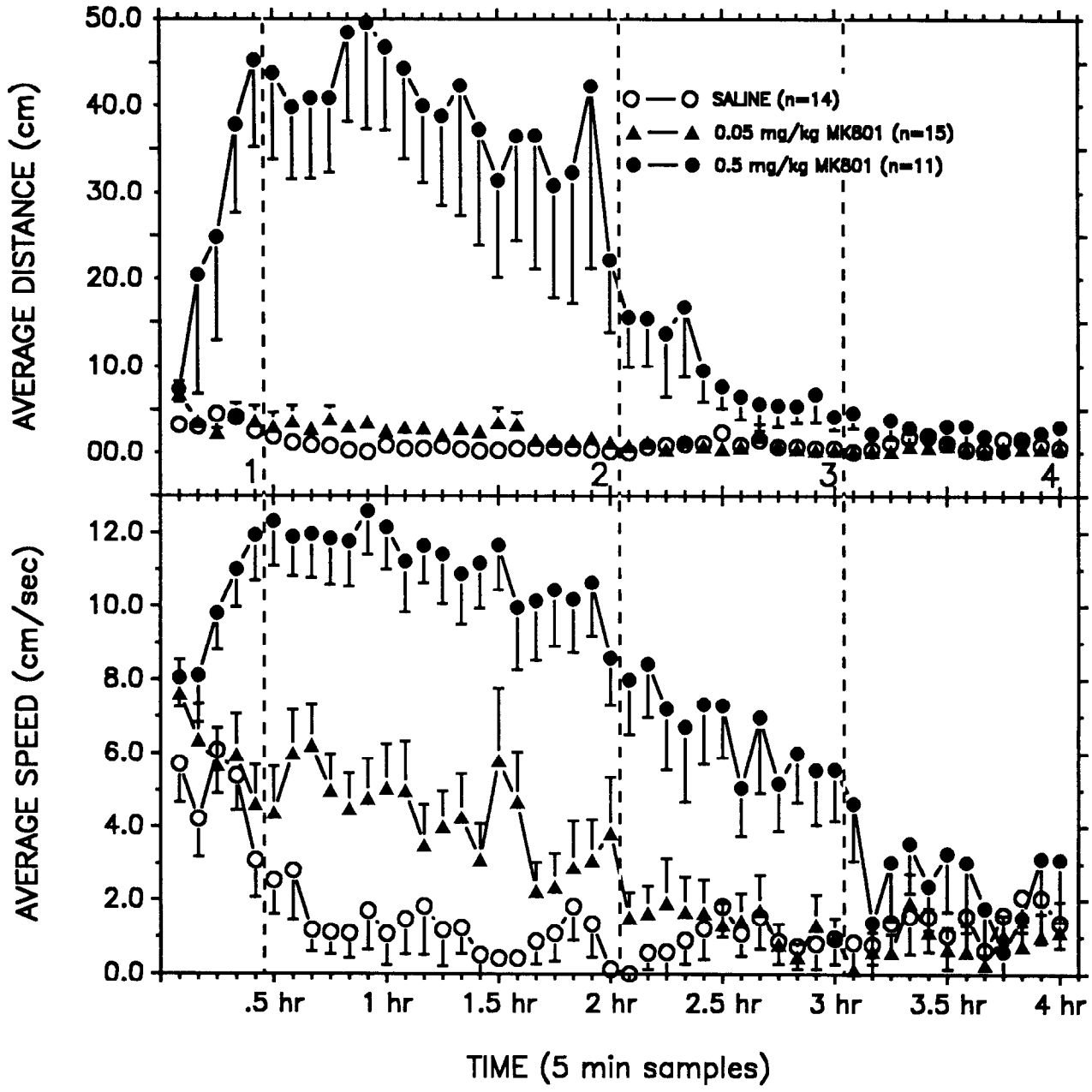

FIG. 1. Duration of MK801-induced hyperactivity, as measured by AD (top portion) and AS (bottom portion), in 5-min samples. Data collection was initiated at time zero, immediately following individual injections. Open circles represent mean data from the saline-treated rats (n = 14). Filled triangles represent mean data from the 0.05 mg/kg-treated rats (n = 15). Filled circles represent mean data from the 0.5 mg/kg-treated rats (n = 11). Dashed vertical lines represent divisions between the four identified phases of MK801 induced activation. Note that both measures exhibit an extended plateau pattern of activation during the second phase (see the Results section). Error bars represent SEM. The mean data from the 0.10 mg/kg-treated rats are not shown for reasons of clarity (but see Fig. 3).

diate ascension in activity at the 0.5 mg/kg dose. In contrast, the lower doses exhibited more mild and delayed increases, and for some measures exhibited actual decreases during the first phase. In this latter case, where the lower doses showed decreases, the saline controls showed similar trends, $F(1, 13) < 5.791, p > 0.032$; AS, suggesting that the injection procedure may have prompted a brief exploratory bout at the start of the recording session. The vertical measures also exhibted decreases, which may have been related to an exploratory bout, or alternately may reflect motor deficits in rearing. The data presented in Figs. 1 and 2 are consistent with these analyses.

During the second phase, the measures of TD, AD, AS, NM, MT, and VM exhibited effects of dose, $F(1, 50) < 19.02, p < 0.0005$; AD, while of those measures TD, AD, NM, and MT exhibited dose by sample interactions, $F(3, 50) > 3.870, p < 0.014$; TD. In accordance with these results, at the level of individual doses, the measures that had showed no

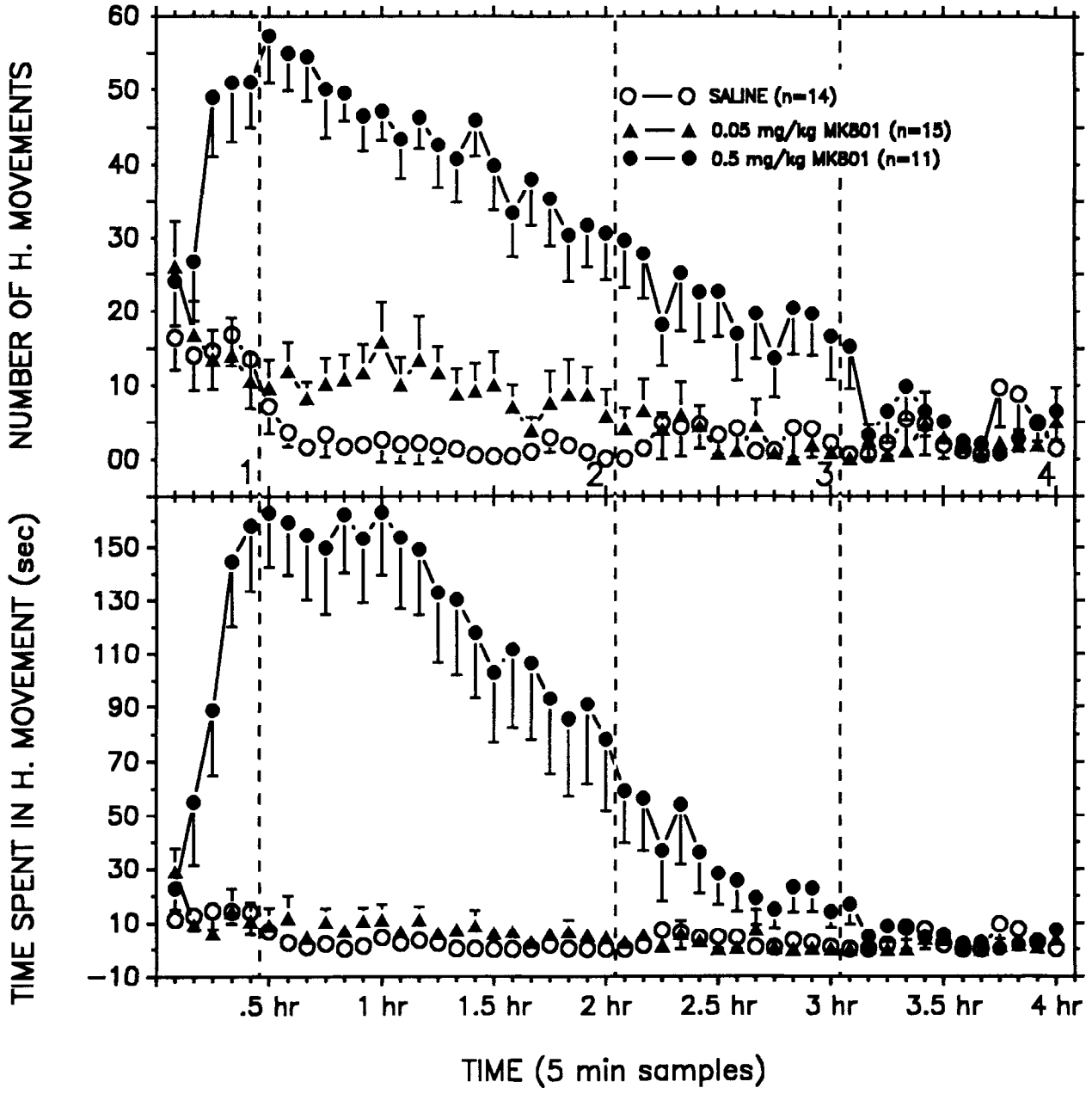

FIG. 2. Duration of MK801-induced hyperactivity, as measured by NM (top portion) and MT (bottom portion). Details and denotations the same as Fig. 1. Note that NM exhibits a continual decline of activity, once peak activity occurs at 30 min postinjection, while MT exhibits a partial plateau of increased activity during the second phase (see the Results section).

change between the doses across the 18 samples either exhibited no trends (VM), or exhibited consistent linear trends (and no nonlinear trends) at all doses (AS). Of the remaining measures (TD, AD, NM, MT), at the lower doses only, NM showed a significant trend, which was linear in nature, $F(1, 14) = 5.7701$, $p = 0.031$; NM at 0.1. All other measures at the 0.05 mg/kg and 0.1 mg/kg MK801 doses exhibited no significant trends across the 18 samples. At the 0.5 mg/kg dose TD, AD, and AS failed to exhibit trends across the 18 samples. The remaining measures at the highest dose exhibited declining linear trends, $F(1, 10) > 7.302$, $p < 0.022$; MT, or no change (VM, VT). These findings indicate that siginificant differences were maintained between the doses on all but the vertical measure of VT. The nonsignificant trend analyses for the individual doses of VM, in conjunction with the overall nonsignificant dose effect for VT, could be interpreted as the presence of motor deficits in rearing that could not easily be seen against the backgound of basal or floor levels of rearing activity recorded from the saline-treated rats. Trend analyses for the lower two doses of MK801 for the remaining nonvertical measures indicated gradual linear declines (AS, NM) or no change at all (TD, AD, MT). The same analyses performed on

the highest dose revealed that a plateau of activity occurred for the measures of TD, AD, and AS, while the remaining measures at this dose exhibited steady declines (NM) or a short plateau followed by a sharper decline (MT). The data presented in Figs. 1 and 2 reflect these different plateau durations of the high dose.

During the third phase, the nonvertical measures (TD, AD, AS, NM, MT) exhibited dose effects, $F(3, 50) > 6.72$, $p < 0.001$; TD, and dose by sample interactions, $F(3, 50) > 7.485$, $p < 0.0005$; TD. The vertical measures (VM, VT) showed neither dose effects nor dose by sample interactions. When individually examined across samples only the 0.5 mg/kg MK801 dose exhibited any significant trends, of which both linear and quadratic were often significant, but with the linear trend typically stronger, $F(1, 10) > 6.201$, $p < 0.032$; NM, quad. Although none of the measures exhibited significant trends for the lower doses of MK801, the linear trend for the measure of AS, at the 0.1 mg/kg dose, approached significance, $F(1, 13) = 3.947$, $p = 0.068$. Thus, during the third phase, activity levels of the lower dose groups became equivalent to those of the saline-treated rats. Further, at the high dose, all nonvertical measures were declining throughout this phase as seen in Figs. 1 and 2.

No significant effects during the fourth phase were found for any measure at any dose. Thus, during the final phase, all groups exhibited equal levels of activity, indicating that even the rats treated with the highest dose of MK801 had returned to the baseline levels of the saline-treated animals.

Final post hoc examination of group means for individual samples confirmed the above analyses. For the vertical variables of VM, VT, only three samples exhibited differences out of the pooled 192 samples examined, and these were present only during the second phase, with the differences being between the 0.5 mg/kg dose and the remaining groups. For the nonvertical activity measures, differences between the groups began either on the second or third sample, and were between the 0.5 mg/kg group and the other means, which remained consistent throughout the three phases (samples 3-38). Differences between the 0.05 mg/kg and 0.1 mg/kg doses of MK801 were observed once for AS at the very end of the second phase (sample 23), but not for any of the other measures on any of the samples tested. However, a number of differences were found for the activity measures of AD and AS either between the 0.05 mg/kg MK801 dose and the saline group (AD = 3 samples, AS = 7 samples) or between the 0.1 mg/kg MK801 dose and the saline group (AD = 4 samples, AS = 5 samples). These differences were all confined to the second phase, as illustrated in Fig. 3. In accordance with the above analyses, none of samples in the fourth phase exhibited any differences for any of the measures.

DISCUSSION

These results indicate that MK801 induced hyperactivity in a dose-dependent fashion, although it should be noted that the lower two doses were not statistically differentiated from each other. However, these same doses (0.05 mg/kg, 0.1 mg/kg) were differentiated from the saline controls, albeit during the second phase (see Fig. 3). It is important to emphasize that these differences between the lower doses and saline controls occurred only during the second phase and, therefore, the hyperactivity induced by these doses attenuated sooner than that of the highest dose. These results confirm our earlier findings of hyperactivity at the 0.05 mg/kg dose of MK801,

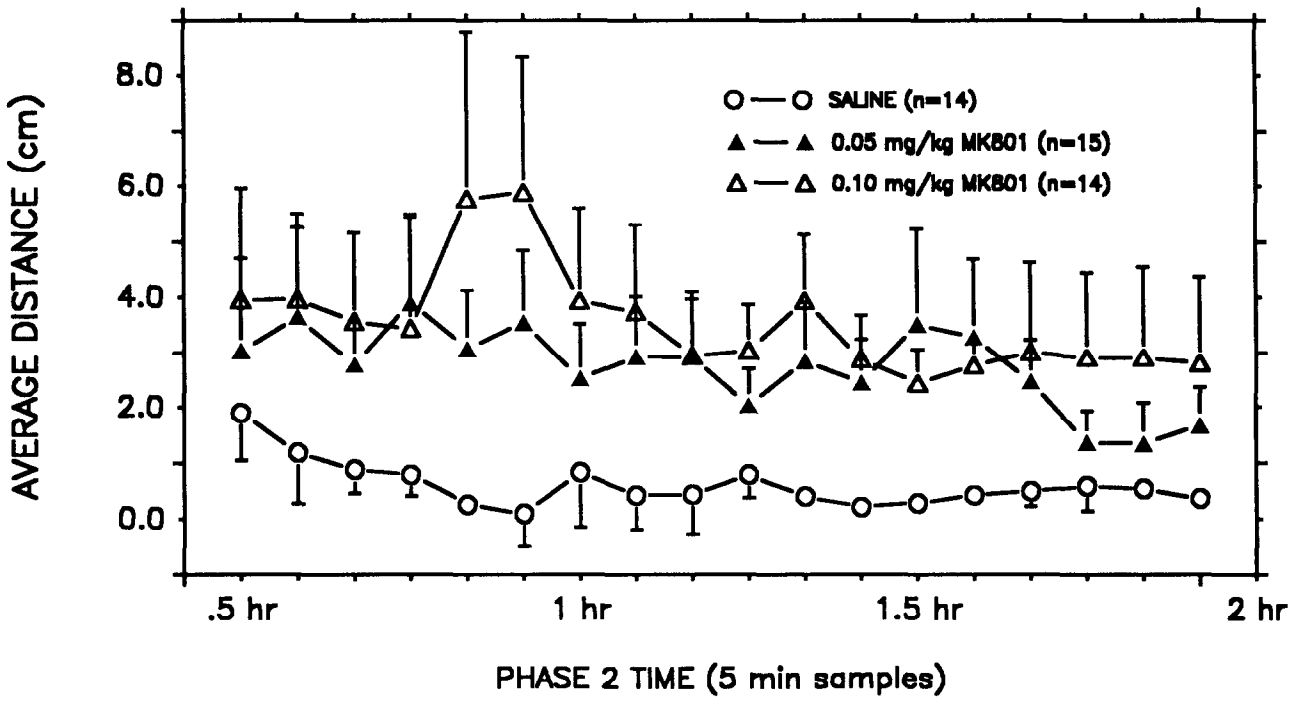

FIG. 3. Focus on the MK801-induced hyperactivity during the second phase of the experiment, for the lower doses, as measured by AD. Note the expanded scale on the vertical axis. Open circles represent mean data from the saline-treated rats ($n = 14$). Filled triangles represent mean data from the 0.05 mg/kg-treated rats ($n = 15$). Open triangles represent mean data from the 0.10 mg/kg-treated rats ($n = 14$). Note the degree of overlap between the activity levels of the rats treated with 0.05 and 0.10 mg/kg of MK801 (see Results).

when the more sensitive paradigm of exploratory activity combined with a within-subjects repeated administration design was employed (11). Evidence of hyperactivity at the 0.05 mg/kg dose has also been found using different methods (23,24). Results from this study are also in partial agreement with those of the previous attempt to chart the duration (7). During the peak activity plateau, the absolute values of the measures AD and AS were quite comparable, with the average distance per movement at approximately 40 cm and the average speed within 2 cm/s of levels previously found (7), at 12 cm/s. Conversely, results from this study also appear partially at odds with the previous attempt to chart the duration (7). Presently, the peak activity was found to occur 30 min following MK801 administration, whereas previously, the peak was found to occur 60 min following administration. These differences may be explained by the 5-min sample periods used here vs. the 15-min sample periods used earlier (7). Thus, if the data from the 5-min samples were aggregated into 15-min clusters, a rightward shift of the peak activity would occur approximately 1 h after the MK801 injections. Given the finer resolution of the 5-min samples over the 15-min samples, and given the larger sample size of 11 over 6, the present results should be both more accurate and reliable in determining the peak of MK801-induced hyperactivity.

Hyperactivity induced by the 0.5 mg/kg dose of MK801 attenuated to the level of saline controls approximately 180 min (3 h) following MK801 adminstration. The pattern of activity decline following the peak varied, dependent upon the measure examined.

Although the absolute values of the measures presented here match those reported by others (7), the lower doses used here do not match well with our own earlier findings (11), in that previously higher levels of activity and vertical impairments were found at the 0.05 mg/kg dose. This may be again accounted for by differences between the exploratory vs. basal activity paradigms. Thus, the exploratory paradigm may interact with the use-dependent nature of MK801, such that the activity was exaccerbated. Conversely, vertical deficits may not be as readily apparent in the current basal paradigm, since the saline-treated controls may already have been at floor levels of vertical activity. As such, any deficits induced by MK801 may not have registered as strongly as before (11).

Although MK801-induced hyperactivity has been now well established, even at doses as low as 0.05 mg/kg, this effect has been suggested to wane with repeated administration (5,20). Previously, we found no differences in hyperactivity at 0.05 mg/kg between groups that received it as the first dose of an ascending series or the third dose of a descending series (11). However, the observations referred to (5,20) involved repeated administration over many days of an equally low dose (0.0625 mg/kg). Formal measurements of a high dose (0.5 mg/kg) (8) have partially supported the waning of activation after repeated adminstration, with rearing deficits and thigmotactic behavior recorded on the first day of MK801 administration greatly attenuated after 21 days of chronic adminstration. Yet, horizontal ambulatory scores in this same study remained elevated (8). These results may be accounted for by differences in dose.

In conclusion, this study has four main results. First, that hyperactivity is one of the behavioral consequences of a single administration of MK801. Second, the peak of the MK801-induced hyperactivity occurs approximately 30 min after administration. Third, the duration of the MK801-induced hyperactivity is approximately 3 h, and fourth, that MK801-induced hyperactivity occurs at doses as low as 0.05 mg/kg. The extent to which these effects may or may not interact with observed learning deficits, and may or may not be a general characteristic of NMDA antagonists, is still part of an ongoing debate (4,5,9,11,13–15,18,21).

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