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Comparison of error patterns produced by scopolamine and MK–801 on repeated acquisition and transition baselines

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Abstract. An understanding of the differential role of cholinergic and glutaminergic systems may be limited by the failure to move the analysis of learning impairments beyond an assessment of changes in overall accuracy. This paper reports the results of two studies in which the effects in rats of scopolamine (0.5–3.0 mg/kg IP), a cholinergic antagonist, and MK–801 (0.05–0.3 mg/kg IP), an NMDA-receptor antagonist, were compared in two different repeated learning procedures and the nature of the underlying error patterns produced by each was evaluated. The first study examined drug effects upon a repeated sequence acquisition procedure and found that while both drugs decreased overall accuracy in a dose-dependent manner, the predominant error pattern varied significantly with drug; scopolamine primarily produced skipping errors within the sequence, whereas MK–801 more prominently increased perseveration on the first and second members of the sequence. In the second study, which used a repeated transition procedure, both drugs again significantly decreased overall accuracy in a dose-dependent manner, but no consistent differences in error patterning produced by the drugs were observed. Thus, while both cholinergic and NMDA systems play a role in learning, the behavioral processes underlying the changes in overall accuracy may differ, as indicated by the differential patterns of errors produced by scopolamine and MK–801 in the repeated acquisition baseline. Furthermore, the observed differences in the underlying behavioral processes of scopolamine and MK–801 in the repeated acquisition but not on the repeated transition procedure suggest that each of the two drugs may affect more than one of the variables controlling behavior, with the relative impact of drug-related changes in controlling variables depending upon the operative contingencies of the learning task.

Key words: Learning – MK–801 – Rats – Repeated acquisition – Repeated transitions – Scopolamine

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Several different neurotransmitter systems have been implicated as neurochemical mediators of learning processes. Prominent among these are both the cholinergic and glutam-atergil systems, the latter via the N-methyl-D-aspartate (NMDA) receptor complex. Deficits in cholinergic neurotransmitter systems are considered a likely source of learning and memory impairments resulting from Alzheimer's disease (Drachman 1977; Levy et al. 1984). Recent evidence suggests that glutam-atergil pathways in the hippocampus may also play a role in learning processes, through the long-term enhancement of postsynaptic responses following high rates of neuronal stimulation (Butelman 1989; Cotman et al. 1989). Consistent with this, noncompetitive NMDA receptor antagonists such as MK–801 have been reported to impair spatial learning tasks that depend upon hippocampal function (e.g. Butelman 1989).

Learning might be described simply as behavior in transition. Studies examining the relationships between neurotransmitter systems and learning have often been limited by the rapidity with which the behavioral response is acquired. That is, once the subject masters the task or problem to be solved, performance of a learned response, rather than learning per se, is being measured. This makes it difficult to generate dose-response functions in individual organisms or to investigate the role of drugs or treatments with delayed, cumulative, or long-lasting effects. Two types of procedures, repeated acquisition and reversal learning tasks, have been used in the past to overcome some of these problems.

The repeated acquisition procedure originally described by Boren (1963) provided a method by which transition states could be repeatedly evaluated over time within a single subject by requiring an organism to learn a different sequence of responses during each experimental session. Cholinergic agents, including scopolamine, have been shown to impair response sequence acquisition by increasing errors within and between sequences in rats (Howard and Pollard 1983), monkeys (Levy et al. 1984; Penetar 1985), and humans (Higgins et al. 1989). Phencyclidine, a noncompetitive NMDA-

receptor antagonist, has also been reported to impair acquisition of response sequences in both monkeys (Thompson et al. 1983), and pigeons (Thompson et al. 1986), although the pattern of errors it produces has not been clearly defined.

In reversal learning procedures, the association between a particular response and reinforcement is reversed each time some accuracy criterion is achieved. These paradigms have also been shown to be sensitive to drug intervention, including reserpine (Palfai et al. 1983), as well as cholinergic antagonists such as scopolamine (Soffie and Lamberty 1987).

While it has been demonstrated then, that both cholinergic and NMDA receptor agents can retard learning as reflected in repeated acquisition and reversal learning paradigms, the precise behavioral processes by which this occurs have not been systematically examined. In most such studies, the assessment of overall accuracy has served as the sole measure of a compound's effect. Yet, the types of errors produced by drugs that impede learning may differ substantially, providing clues both to the fundamental behavioral processes at work and to differences in the neurochemical bases of learning deficits. Differentiation of the behavioral processes underlying learning should result in a greater understanding of the differential roles of the various neurotransmitter systems involved. A potential way to achieve this goal is to compare the specific types of error patterns underlying the decrements in overall accuracy produced by these drugs.

This study compared the patterns of errors produced by administration of scopolamine, a muscarinic cholinergic antagonist, and MK–801, a noncompetitive glutamatergic NMDA-receptor antagonist in a repeated acquisition procedure and in a repeated transition task. Its results suggest both that the drugs may have multiple behavioral mechanisms of action and that the common effect of the two drugs in impairing overall accuracy is produced through different underlying behavioral processes in certain learning situations.

Materials and methods

Animals. Male Long-Evans rats, obtained from Blue Spruce Farms (Altamont, NY), at 21 days of age, were housed individually in standard laboratory cages under a 12 h light/dark cycle. Animals were allowed free access to food until they were 55 days of age, at which point behavioral procedures were implemented. Animals were subsequently fed enough food after each daily behavioral session so as to gain 1–5 g/day until they reached 300 g, the value at which body weights were then maintained for the duration of the experiment. Eight rats each were used in experiments 1 and 2.

Behavioral apparatus. Behavioral sessions were conducted in operant chambers (Coulbourn Instruments, Inc., Lehigh Valley, PA) housed in sound-attenuating enclosures ventilated by a fan. Each chamber was equipped with three response levers, which were 3.8 cm above the grid floor and separated by 3.5 cm. A pellet trough, through which 45 mg food pellets (P.J. Noyes Inc., Lancaster, NH) were dispensed, was located below the middle lever. A Sonalert© tone generator was situated above the right lever. Continuous white noise masked extraneous sounds. Behavioral contingencies and data collection were executed by a Digital Equipment Corporation (DEC) PDP 11/73 computer programmed under the SKED–11 system (Snapper et al. 1982). Using this system, the succession of stimulus and response events during each session was stored sequentially with a resolution of 10 ms, permitting the analyses of response rates, patterns of errors, and their relation to schedule contingencies.

Response shaping. Rats were first trained to press each of the three response levers via an autoshaping paradigm used routinely in this laboratory (Cory-Slechta et al. 1985). Reinforcement was programmed for only one lever during each of three successive overnight sessions. Training generally did not require more than three overnight sessions to complete and ensured comparable reinforcement histories on all three levers prior to implementation of the response sequence and response transition procedures. These latter pradigms were then imposed with the following experimental session.

Repeated acquisition procedure. Rats were required to learn a new three-member response sequence during each experimental session. Sequences were randomly presented from among the following two lists: L (Left) R (Right) C (enter), RCL, CLR; or RLC, CRL, LCR. Sequences requiring a repetitive series of responses, e.g. LLR, were excluded to preclude any reinforced history of response perseveration. During one week, sequences would be randomly selected from one list such that no sequence appeared twice in a row. The following week, sequences would be selected from the other list in the same manner. This ensured that sequences were independent from session to session and that each member of the response sequence always differed in its position from the previous session's sequence.

Within a session, rats were required to complete a sequence of three lever presses, for example, LRC, without error in order to obtain a reinforcement. Any error initiated a 2 s timeout period during which the houselight was turned off. Responses occurring during the timeout further extended this period until 2 s had elapsed without a response. Rats were then required to begin the sequence anew. Furthermore, each sequence was coupled to a self-correcting fixed ratio (FR) contingency, such that an error occurring either during a sequence or between sequences would increase the ratio from one to two consecutive errorless sequences for food presentation. Upon completion of two perfect sequences, food delivery occurred and the FR component was reset to one until any new error occurred which then again increased the FR component to two. This titrating FR schedule increased the cost of errors, maximizing the rate of acquisition. All correct responses were signalled by presentation of a tone stimulus. Therefore, given three consecutive correct responses CRL, the tone stimulus would follow depression of each lever. Completion of a sequence was accompanied by the tone and a flash of the foodcup light. Reinforcer deliveries were accompanied by the tone, the foodcup light flash, and the audible click of the pellet dispenser. Sessions continued for 1 h or until 100 reinforcers were delivered, whichever came first, and were conducted 5 days per week (M–F) between 0900 and 1500 hours. Following attainment of stable performance on this baseline, as indicated by ten successive sessions in which 100 reinforcements were delivered within 1 h (approximately 30–40 sessions), effects of drugs upon responding were examined.

Response transition procedure. At the beginning of each experimental session, one of the three response levers was randomly designated as the reinforcing, or "hot" lever, while the two non-reinforcing or "cold" levers were programmed under extinction schedules. After 30 reinforcements were obtained on the hot lever, one of the other two levers was randomly selected to become the reinforcing lever, replacing the initial one. After an additional 30 reinforcers, the third lever became the "hot" lever, replacing the second lever. No external stimulus cues indicated this transition in reinforced levers. The sequence of lever assignments within a session was randomly determined across sessions. Presses on the hot lever were reinforced with 45 mg Noyes food pellets according to a Random Interval 30 s (RI 30″) schedule. On this schedule, the first press occurring after an elapsed interval of time produced food delivery. The length of the interval varied from reinforcer to reinforcer but had a mean value

of 30 s. Responding was also coupled to a self-correcting fixed ratio contingency, such that a response on either cold lever would increase the ratio from one to five consecutive responses on the hot lever for food presentation (FR 5). Upon completion of five presses on the hot lever and completion of the random interval, food delivery occurred and the FR component was reset to one until a new cold lever response occurred which then again increased the FR component to five. This titrating FR schedule increased the cost of errors (cold lever sampling), maximizing acquisition by discouraging frequent lever switches and encouraging persistent responding on one lever. Reinforcer deliveries were accompanied by a foodcup light flash and the audible click of the pellet dispenser. Sessions continued for 2 h or until 30 reinforcers had been earned on each lever and were conducted 5 days per week (M–F) between 0900 and 1500 hours. Following attainment of stable performance on this schedule, designated as ten consecutive sessions in which overall accuracy of 90% (hot lever responding/total responding across all three phases) was recorded within a session for each lever, drug effects on responding were examined. The number of sessions to criterion was not directly evaluated since several parametric manipulations were undertaken before the final parameters described here were implemented.

Drug administration. Rats were injected IP with either physiological saline, or scopolamine hydrobromide (Sigma Chemical Co., St Louis, MO) diluted in physiological saline at doses of 0.5, 1.0, 2.0, or 3.0 mg/kg, 45 min prior to the start of a session. Each dose was tested at least twice in each rat. Following completion of the scopolamine injection series, IP doses of either physiological saline, or 0.05, 0.1, 0.2, or 0.3 mg/kg MK–801 maleate (Research Biochemicals Inc., Natick, MA) diluted in physiological saline were injected 45 min prior to the session. Again, each dose was tested at least twice in each rat.

Doses of both drugs and saline were administered in random order and at a constant volume of 0.25 ml. At least one recovery (control) session was run between each drug or saline session to minimize carry-over effects from a previous day's session. If the rat failed to reach criterion (less than 100 reinforcement/h for the repeated acquisition procedure and failure to obtain, within 2 h, 30 reinforcers on each lever in the repeated transition procedure), additional control sessions were conducted until performance had restabilized. A 2 week period of sessions conducted with no injections occurred between the end of the scopolamine injection series and the beginning of the MK–801 injection series to provide a clearing-out period. No changes in overall accuracy occurred over these intervals, indicating no carry-over of drug effects.

Statistical analyses. Statistical analyses were conducted using the BMDP Statistical Software Package (Los Angeles, CA). Repeated measures analyses of variance (RMANOVA) were conducted for each drug to determine whether there was a main effect of drug dose on overall accuracy or on overall response rate (total lever presses/session length) for both the repeated acquisition and repeated transition procedures.

To determine whether sequence bias played any role in the results obtained in the repeated acquisition procedure, the mean percent correct (defined as number of presses in the proper sequence/total number of presses $\times 100$) was calculated for all saline sessions. Mean saline session data for each of the six sequences were then compared, as a percentage of the grand mean, via Chi square analysis.

Subsequent analyses were aimed at evaluating the particular classes of errors produced by each drug in each procedure. For the repeated acquisition procedure, sequence development and error patterns were examined by calculating the percentage of responses on each lever given a previous correct response on a particular lever. Analyses were conducted on pairs in which the first member of the pair was a correct response, using the following pairs of responses where "1" indicates the first member of the sequence, "2" the second, and "3" the third (within each pair, boldfaced numbers identify a correct response and standard type indicates an error): **1**–1, **1–2**, **1**–3, **2**–1, **2**–2, **2–3**, **3–1**, **3**–2, **3**–3. Therefore, **1–2** indicates that the rat correctly proceeded from the first to the second member of the sequence, **1**–3 indicates a correct first member followed by a skip to the lever representing the third member, while **3**–3 indicates that once a rat correctly responded on the third member of the sequence, it perseverated on that lever rather than beginning the next sequence. A total of at least five response pairs per drug dose was deemed the minimum necessary to include data for a particular subject in the statistical analyses. If an animal did not reach that criterion for a particular response-pair at a particular dose, it was treated as missing data in the statistical analyses and dropped. These pairs of responses were analyzed separately via repeated measures analysis of variance as described above.

The higher doses of MK–801 (0.2–0.3 mg/kg) tended to severely suppress responding. Among response pairs beginning with "**1**", two rats did not produce at least five paired responses in each possible combination, deemed the minimum necessary, and data for these two rats were therefore dropped from the analysis of first member pairs at the 0.3 mg/kg dose. Among response pairs beginning with "**2**", four rats did not produce at least five paired responses in each possible combination at the 0.3 mg/kg dose. Among response pairs beginning with "**3**", five rats did not produce at least five paired responses in each possible combination at the 0.2 mg/kg dose. In cases where more than two rats had missing data at the highest dose, the analyses were run minus that dose, which restored the number of subjects included in those analyses to at least six. Consequently, the sample sizes for each group were 8 for all scopolamine analyses using five dose levels. For MK–801 analyses, $n=6$ for analyses of response pairs beginning with "**1**" using five dose levels, 6 for analyses of response pairs beginning with "**2**" using four dose levels, and 8 for analyses of response pairs beginning with "**3**", using three dose levels. In order to present a clearer picture of the drug effects, however, the figures include data from doses dropped from the statistical analyses.

These error pattern analyses required nine tests for each drug, so that half of the tests would be expected to be significant by chance alone. Given that numerous tests attained very high levels of statistical significance, it was not deemed necessary to impose a correction for the number of tests.

For the repeated transition procedure, analyses were conducted on pairs in which the first member of the pair was either the "hot" lever, represented by a "1", or else one of the two "cold" levers, represented by a "2" or a "3". In order to determine whether cold lever responding was influenced by prior reinforcement history within a session, responases on the cold levers were distinguished in the following manner. "2" was always assigned to the lever which was most temporally distant from association with reinforcement. "3" was assigned to the lever which had been "hot" immediately prior to a hot-lever shift. Therefore, following the first transition, "2" was assigned to responses on the lever which had not yet provided reinforcers, while "3" was assigned to responses on the previously "hot" lever. Following the second transition, "2" was now the lever which first provided reinforcement in that session. "3" was again assigned to the lever which was "hot" prior to the latest reversal. A "1R" was used to represent hot lever responses in which food delivery occurred. As in experiment 1, a total of at least five response pairs per drug dose was deemed the minimum necessary to include data for that rat in the statistical analyses.

In the statistical analyses, decreased response rates at the highest doses of scopolamine resulted in an n of 7 in the phase II (second transition) analyses, and an n of 6 for the phase III (third transition) analyses. MK–801 produced an even larger decrease in responding at higher doses, leaving an n of 5 for phase II analyses, and an n of 3 for the phase III analyses. Eliminating the 0.3 mg/kg dose level from the phase II analyses of MK–801 increased the n to 7. Eliminating the 0.2 and 0.3 mg/kg dose levels from phase III analyses of MK–801 also increased the n to 7. This was deemed preferable to an analysis of the entire dose series based upon the more restricted sample and was consequently implemented. To depict more fully the effects of the drugs, however, behavioral effects at the highest doses are included in Figs. 6 and 7.

Results

Repeated acquisition procedure

Evaluation of sequence bias. No evidence of sequence bias was found. Expressed as percent of the grand mean values, the mean percent correct (±SEM) for each sequence was as follows: RLC = 98 ± 3%, RCL = 103 ± 3%, LRC = 104 ± 3%, LCR = 99 ± 3%, CRL = 87 ± 3%, CLR = 112 ± 4%. Chi square analysis of these data yielded non-significant results [$X_1^2 = 0.0393$, $P > 0.05$]. Therefore, accuracy was comparable across all sequences.

Effects of scopolamine. Rats made significantly more errors per reinforcer, in a dose-dependent manner, when injected with scopolamine 45 min prior to the session. Figure 1A shows the percent of correct responses (expressed for each dose as the percent of saline values) as a function of scopolamine dose. Statistical analyses confirmed that accuracy declined significantly to mean levels of about 70% of control values at the highest doses of scopolamine [$F(4,28) = 17.79$, $P < 0.0001$], with the two highest doses, 2.0 and 3.0 mg/kg, producing a roughly similar impairment of accuracy. Neuman-Keuls post-hoc analyses indicated that all doses differed significantly

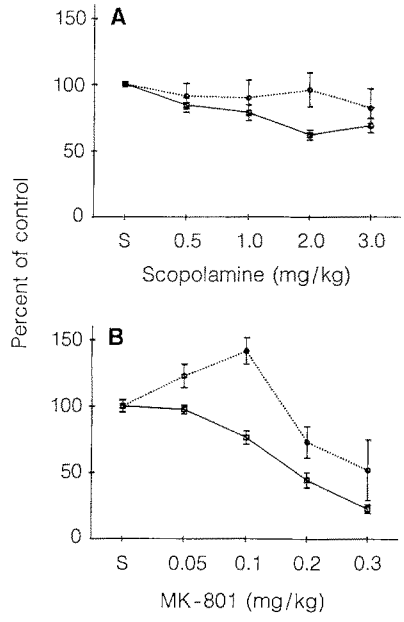

Fig. 1A, B. Effects of scopolamine (**A**) and MK–801 (**B**) upon overall accuracy *(squares)* and response rate *(circles)* expressed as percent of saline values ± standard error. In order of increasing dose, scopolamine mean response data are 39, 36, 36, 36, 32 responses per minute, respectively. MK–801 mean response data are 29, 36, 44, 21, 14 responses per minute, respectively

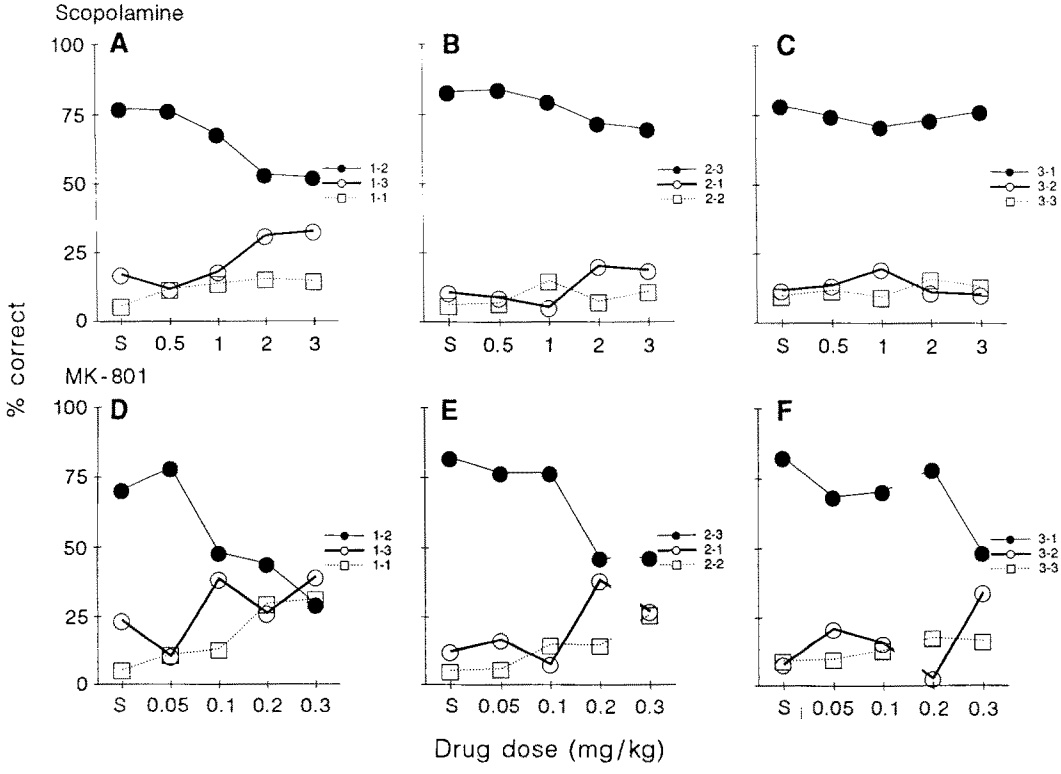

Fig. 2A–F. Percent responding for each response pair as a function of dose of scopolamine *(top panels)* and MK–801 *(bottom panels)*. Panels **A** and **D** present data for response pairs correctly beginning with the first member of the sequence. Panels **A** and **E** show data for response pairs correctly beginning with the second member of the sequence. Panels **C** and **F** present data for response pairs beginning with the third member of the sequence. Within this figure, there were 8 rats per dose of scopolamine (panels **A–C**). Breaks in curves for MK–801 data refer to doses above which were not included in the statistical analyses. There were 8 rats per dose of MK–801 except for the 0.3 mg/kg dose in panel **D** ($n = 6$) and panel 5 ($n = 4$). The 0.2 mg/kg dose level in panel **F** consisted of three rats, and the 0.3 mg/kg dose consisted of two rats

Table 1. Repeated measures analyses of variance for response pairs beginning with a correct response

Scopolamine			*MK-801*		
Response Pair	F[a]	P	Response Pair	F	P
1–1	6.83	0.0006	**1**–1	10.14[b]	0.0001
1–**2**	11.46	<0.0001	**1**–**2**	8.54[b]	0.0003
1–3	7.87	0.0002	**1**–3	4.19[b]	0.0126
2–1	8.30	0.0002	**2**–1	3.47[c]	0.0429
2–2	5.13	0.0031	**2**–2	4.06[c]	0.0268
2–**3**	9.89	0.0001	**2**–**3**	7.72[c]	0.0024
3–**1**	1.25	0.3136	**3**–**1**	4.83[d]	0.0254
3–2	2.01	0.1208	**3**–2	5.87[d]	0.0180
3–3	2.36	0.0771	**3**–3	2.63[d]	0.1070

[a] $df=4,28$; [b] $df=4,20$; [c] $df=3,15$; [d] $df=3,18$; [e] $df=2,14$

from saline ($P<0.002$ for each). This decline in accuracy occurred despite the fact that response rate was largely unaffected by the same doses of scopolamine [$F(4,28)=0.54$, $P=0.705$] (see Fig. 1A).

The error patterns generated by scopolamine are presented as a function of dose in Fig. 2 and results of the corresponding statistical analyses are presented in Table 1. Scopolamine caused similar types of errors across all subjects. These analyses revealed that the impairment of overall accuracy was primarily due to the decline in a correct first member of the sequence being followed by a correct second member (**1**–**2**; panel A), dropping from about 77% of all two-response pairs at control levels to 52% at the highest scopolamine dose. While there was some tendency for perseverative responding on the first member to occur (**1**–1), increasing by about 9%, the most significant effect was the propensity of scopolamine to increase the frequency of a first sequence member being followed by the final member, i.e. skipping the correct second response (pair **1**–3), which increased from a level of approximately 17% to nearly 35%. Once the second member of a sequence was successfully reached (panel B), scopolamine significantly reduced accuracy in proceeding to the third member (**2**–**3**) by slightly increasing perseveration (**2**–2; about a 7% increase), but to a greater extent by incorrectly returning to the first member of the sequence (**2**–1; about an 11% increase). In general, however, effects on the second member responses were less pronounced than on the first member responses. There was no evidence for an effect following completion of a sequence (panel C), as none of these dependent variables demonstrated significant differences (no change in **3**–**1**, **3**–2, or **3**–3). In essence, then, the primary effect of scopolamine was to increase skipping responses during a sequence (**1**–3, and **2**–1; total increase of 28%). Perseverative responding increased as well, but to a lesser extent (**1**–1 and **2**–2, up 17%).

To determine whether scopolamine increased skipping errors to a significantly greater extent than perseverative errors within sequences, the percentage of two-response pairs which were skipping errors (**1**–3 and **2**–1) and perseverative errors (**1**–1 and **2**–2) were pooled and compared using a mixed design analysis of variance (with drug dose serving as repeated measure and error type serving as a between subjects variable). Data for this analysis are presented in Fig. 3 (top panel). As expected, the main effect of drug dose was significant [$F(4,56)=13.47$, $P<0.0001$], reflecting the effect of increasing scopolamine dose on overall accuracy. The main effect of error type (skipping versus perseverative) was also significant [$F(1,14)=13.47$, $P<0.003$], thus indicating that, overall, significantly more skipping errors were occurring than were perseverative errors. More importantly, the Dose × Error type interaction was significant [$F(4,56)=15.08$, $P<0.0001$], confirming the more pronounced increase in skipping errors compared to perseverative errors across dose of scopolamine.

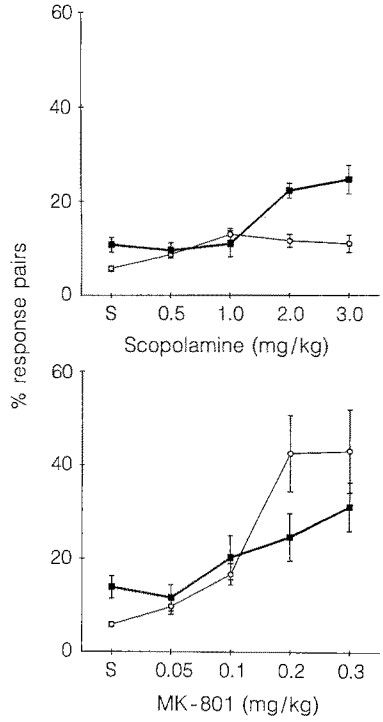

Fig. 3. Type of error produced as a function of dose for scopolamine *(top)* and MK-801 *(bottom)* ± standard error. Percentages are the proportion of all pairs of responses consisting of a correct lever press followed by either a perseverative error *(open circles)* or a skip error *(closed squares)*

Effects of MK-801. MK-801 also interfered with acquisition of response sequences (Fig. 1B). Rats made significantly more errors per reinforcement, in a dose-dependent manner, when injected with MK-801 45 min prior to the session [$F(4,28)=45.04$, $P<0.0001$]. Neuman-Keuls analyses indicated that each dose differed significantly from saline (0.1 mg/kg, $P=0.017$; 0.2 and 0.3 mg/kg, $P<0.0001$) with the exception of the lowest dose (0.5 mg/kg, $P>0.10$). Overall accuracy declined to 53% of control values at the highest dose.

In contrast to scopolamine, MK-801 resulted in an inverse U-shaped dose effect function for response rate, increasing response rates at doses up to 0.1 mg/kg and decreasing rates thereafter (Fig. 1B). RMANOVA in-

dicated significant differences in response rates across dose [$F(4,28)=9.12$, $P=0.0001$], and orthogonal decomposition indicated a significant quadratic component [$F(1,7)=15.45$, $P<0.006$] in conjunction with this pattern of response rate changes.

The effects of MK–801 on various two-lever response pairs are presented by dose in Fig. 2 (Panels D–F) and results of the corresponding statistical analyses are presented in Table 1. As with scopolamine, MK–801 caused similar types of errors across all subjects, but the type of error differed from scopolamine, being primarily perseverative in nature.

A significant decrease in accuracy was observed in the percentage of **1–2** response pairs, i.e., a correct first response proceeding to a correct second response, declining from approximately 70% under control conditions to about 30% at 0.3 mg/kg MK–801 (Fig. 2, panel D). While this was, in part, due to an increase of 15% in the percentage of **1**–3 pairs (skipping the middle member), MK–801's largest effect at this point in the sequence was to cause a sixfold increase in the percentage of **1**–1 response pairs (perseveration), from 5% to approximately 30%.

MK–801 also significantly reduced accuracy following correct second member responding (Fig. 2, panel E), with percent **2–3** response pairs declining from 82% to 47% at 0.3 mg/kg. In this respect, then, MK–801 was more potent than scopolamine (cf panels A and B of Fig. 2). An inconsistent but significant increase in returning to the first member of the sequence (**2**–1; from 13% to 27%) was observed. The deline in accuracy at this point in the sequence, however, was again primarily due to the increase in perseverative errors (**2**–2) from roughly 5% to 26%. In summary, MK–801's primary effect within a sequence was to increase perseverative responding (response pairs **1**–1 and **2**–2, up 50%), while increasing skipping responses to a lesser extent (**1**–3 and **2**–1; up 35%).

To confirm that MK–801 indeed increased perseverative errors to a significantly greater extent than skipping errors within sequences (Fig. 3b), these two types of errors were pooled and analyzed via mixed design analysis of variance as above. The main effect of drug dose was significant [$F(4,40)=17.49$, $P<0.0001$], reflecting the effect of increasing MK–801 dose on overall accuracy. While the main effect of error type (skipping versus perseverative) was not significant [$F(1,10)=0.47$, $P=0.514$], the Dose × Error type interaction was [$F(4,40)=3.28$, $P<0.021$], confirming the greater increase in perseverative errors relative to skipping errors with increasing dose of MK–801.

The transition from completion of a non-reinforced sequence to the beginning of a new sequence was also disrupted by MK–801 (Fig. 2, panel F). There was a decline from 83% to 49% in the proportion of third member to first member responses (**3–1**). Statistical analysis indicated that this was generally due to an inconsistent, but ultimately strong increase in **3**–2 responding.

Response transition procedure

Effects of scopolamine. Cold lever sampling increased significantly, in a dose-dependent manner, following injections of scopolamine 45 min prior to the session, resulting in a decline in overall accuracy as shown in Fig. 4A which presents percent of hot lever responses (expressed as percent of saline control) plotted in relation to the dose of scopolamine [$F(4,28)=8.44$, $P=0.0001$]. Each dose differed significantly from saline ($P<0.002$) with the exception of the 0.5 mg/kg dose ($P=0.443$). Overall accuracy declined to levels of about 70% of control at the three highest doses. Effects on response rate paralleled those on accuracy, declining to approximately 80% of control values at the highest dose. The high individual variance in response rate, however, negated the significance of the latter effect [$F(4,28)=2.13$, $P=0.103$; see Fig. 4A).

To further examine the nature of the decline in overall accuracy, the functions relating percent responding on the cold levers as a function of the time since the last reinforcement delivery on the hot lever were plotted for saline and scopolamine sessions (Fig. 5A). As might be expected, cold lever sampling increased in frequency with time since the last reinforcement delivery on the hot lever under saline conditions, generating a relatively curvilinear function (RMANOVA, dose × post-reinforcement interval in 25 s blocks; main effect of block, [$F(4,20)=11.41$, $P=0.0001$]. Scopolamine administration significantly modified this function [$F(4,20)=4.81$,

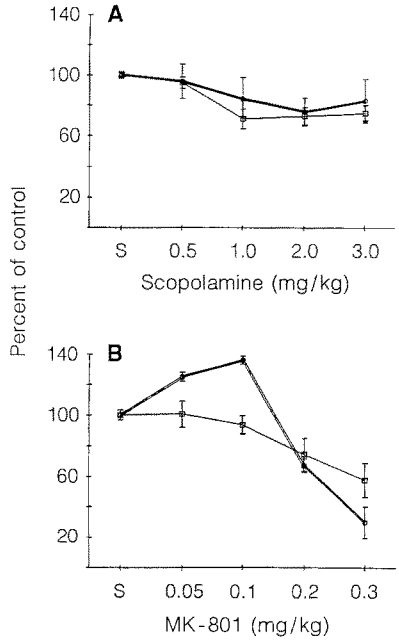

Fig. 4A, B. Effects of scopolamine (**A**) and MK–801 (**B**) upon overall accuracy *(squares)* and response rate *(circles)* expressed as percent of saline values ± standard error. Accuracy was defined as percent of all responses on the reinforcing lever across all three phases. In order of increasing dose, scopolamine mean response data are 75, 70, 56, 54, 56 responses per minute, respectively. MK–801 mean response data are 78, 98, 106, 51, 18 responses per minute, respectively

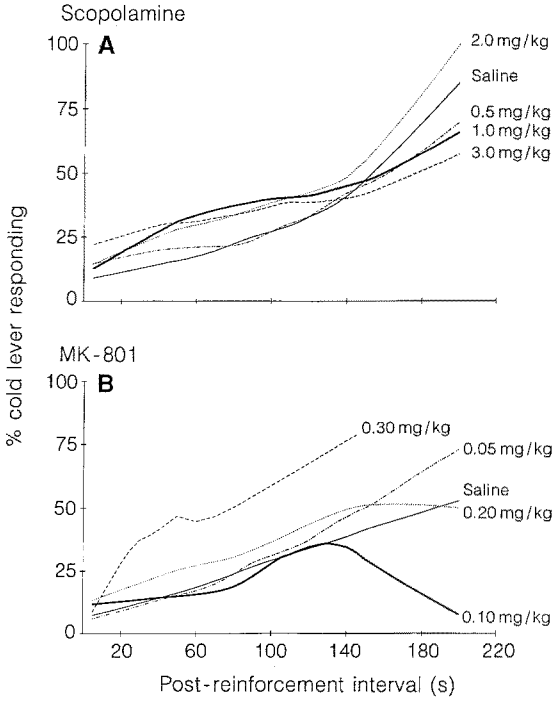

Fig. 5A, B. Percent cold lever responding by dose of scopolamine (**A**) and MK–801 (**B**) as a function of time since last reinforcement. Data were smoothed to increase clarity using locally weighted regression scatter plot smoothing (Chambers et al. 1983)

$P = 0.007$], resulting in an upward shift of this function out to time values of 140 s. For example, during saline sessions, approximately 9% of responses were on a cold lever when less than 5 s had elapsed since the last reinforcer was delivered. After administration of 3.0 mg/kg scopolamine, such sampling had increased to approximately 21%. When 90 s had passed since the last reinforcement, cold lever responses during saline sessions increased to about 25%, whereas corresponding figures ranged between 32% and 38% for the three highest doses of scopolamine. At the higher post-reinforcement intervals, the inverse effect was obtained, which may have resulted from periods of long pauses induced by the drug, which allowed the programmed random intervals to elapse.

Because a statistically significant effect of scopolamine upon overall accuracy was obtained, response pairs were analyzed to determine the behavioral processes responsible for the nature of the decrease. Figure 6 depicts the percent responding for the various response pairs in phase II, the second transition of the session, and Fig. 7 shows corresponding data for phase III, the third and final transition of the session. Results of all corresponding statistical analyses are presented in Table 2.

Phase II responding. Following the first transition (lever switch), scopolamine caused a slight but significant de-

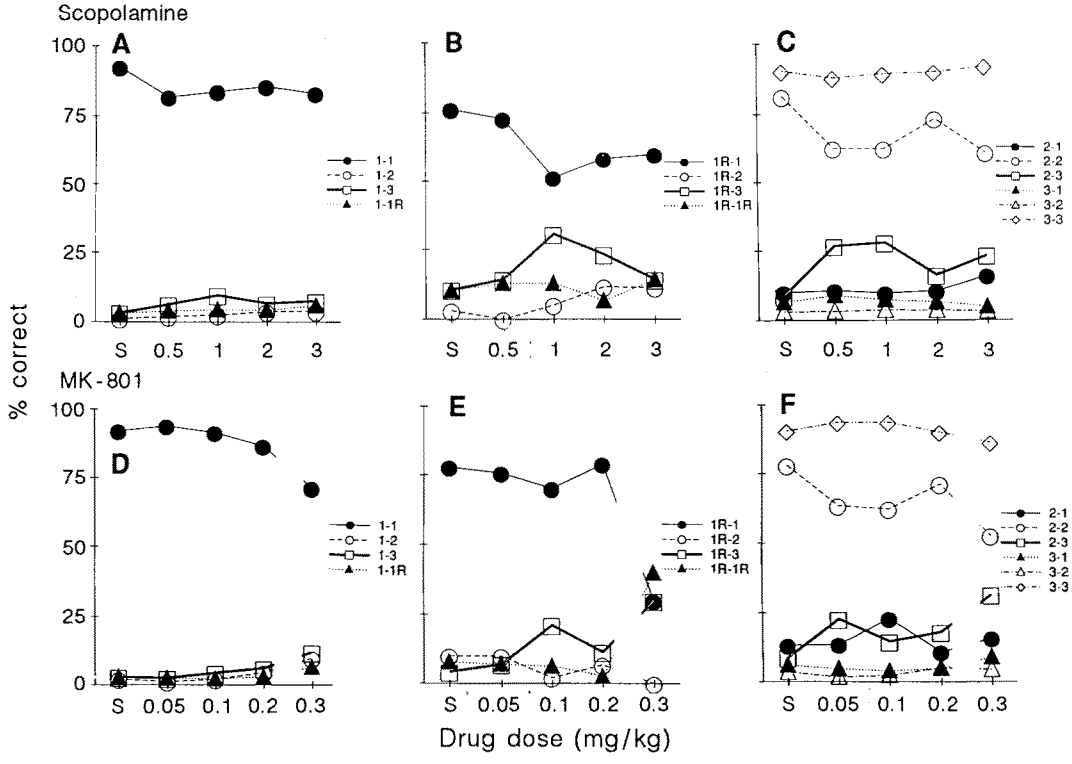

Fig. 6A–F. Percent responding for each response pair during phase II as a function of dose of scopolamine *(top panels)* and MK–801 *(bottom panels)*. In each figure, "1" represents unreinforced hot lever responses for that phase, "1R" represents reinforced responses for that phase, "2" represents responses on the lever which will become the reinforcing lever in the next phase (phase III), "3" represents responses on the lever which was the reinforcing lever in the preceding phase (phase I). Breaks in curves for MK–801 data refer to doses above which were not included in the statistical analyses. There were 8 rats per dose of scopolamine except the 3.0 mg/kg dose ($n = 7$). There were 8 rats per dose of MK–801 except the 0.2 mg/kg dose ($n = 6$) and the 0.3 mg/kg dose ($n = 5$)

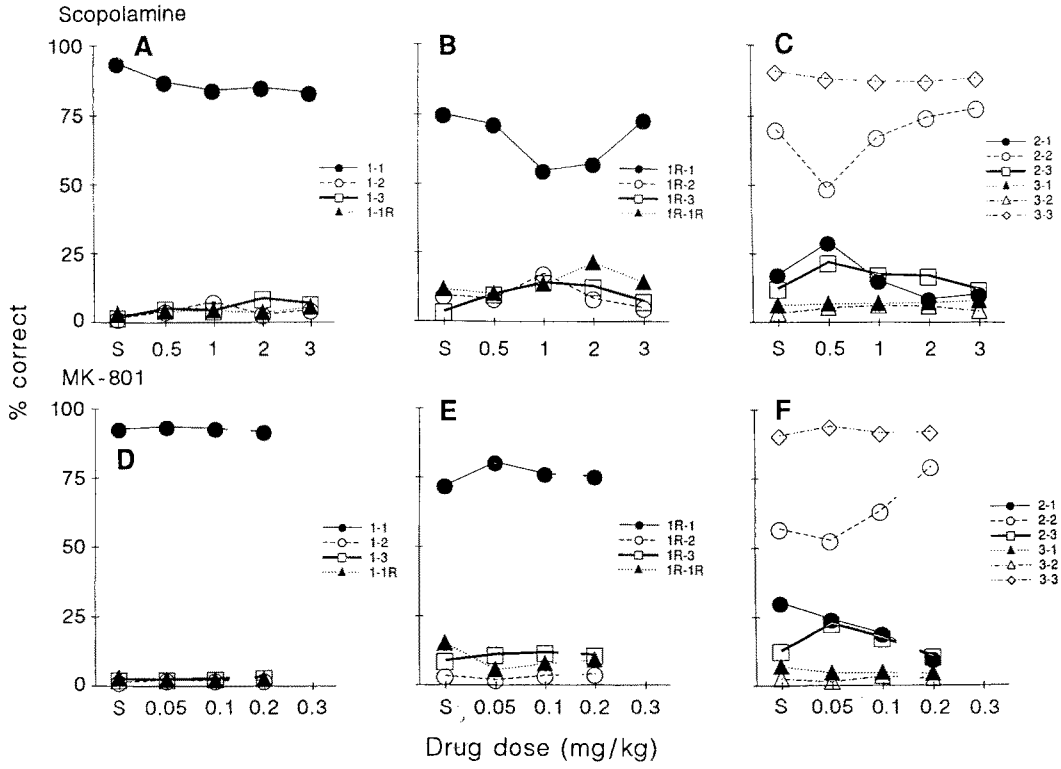

Fig. 7A–F. Percent responding for each response pair during phase III as a function of dose of scopolamine *(top panels)* and MK–801 *(bottom panels)*. In each figure, "1" represents unreinforced hot lever responses for that phase, "1R" represents reinforced responses for that phase, "2" represents responses on the lever which served as the original (phase I) reinforcing lever, "3" represents responses on the lever which was the reinforcing lever in the preceding phase (phase II). Breaks in curves for MK–801 data refer to doses above which were not included in the statistical analyses. There were 8 rats per dose of scopolamine except the 3.0 mg/kg dose ($n=6$). There were 8 rats per dose of MK–801 except the 0.2 mg/kg dose ($n=5$) and the 0.3 mg/kg dose ($n=3$)

cline in the proportion of 1–1 (hot-hot) response pairs, decreasing from 92% to 83% of response pairs beginning with "1" (panel A of Fig. 6). This decline was offset by increased sampling on the other two levers. Of these, the largest increase was in the proportion of 1–3 response pairs, i.e. returns to the previously hot lever, increasing from 3% to approximately 7.5% of the total.

Scopolamine caused a more pronounced decrease in hot lever perseverative response pairs following a reinforcement (1R–1), which declined from 76% to 60% (panel B of Fig. 6). This decrease was not, however, offset by any statistically significant increase in any other response pairs.

Following a response on either cold lever, scopolamine did not produce any systematic pattern of errors (pairs beginning with 2 or 3; panel C of Fig. 6). While the statistical analyses indicated a significant effect on perseveration on the previously hot lever (3–3), it was not dose related. Interestingly, there was no tendency to return to the hot lever following a cold lever response (2–1 or 3–1).

Phase III responding. Panels A–C of Fig. 7 present mean changes in response pairs by dose of scopolamine for the third transition. At this point, scopolamine again caused a slight but significant decline in the proportion of 1–1 response pairs, decreasing from 93% to 83% of response pairs beginning with "1" (panel A of Fig. 7; Table 2). As was the case during phase II, this decline was offset by increased sampling on both of the cold levers. The biggest increase was again in the number of 1–3 response pairs, in which the subject returned to the previously hot lever. The percentage of these response pairs increased from 2% to 8.7% at 2.0 mg/kg before settling at 6.8% at the 3.0 mg/kg dose. There were no significant changes in response pairs beginning with "1R" related to dose during this phase (panel B of Fig. 7).

There was a significant decline in the percent of returns to the hot lever given a response on the original (phase I) hot lever (2–1; panel C of Fig. 7), which declined from 17% to 10%. This was offset by an increase in 2–2 responding, i.e. perseveration on the phase I hot lever, from 70% to 82%. There was no discernible effect upon responding given an initial response upon the phase II hot lever (response pairs beginning with "3").

Effects of MK–801

MK–801 administration also interfered with acquisition of responding on the correct or "hot" lever, however, the nature of the effect was not quite as systematic as was the case with scopolamine. As can be seen in Fig. 4B, overall accuracy declined (as a percent of saline control), in a dose-dependent manner, following injections of MK–801 45 min prior to the session, an effect that was more

Table 2. Analyses of variance for scopolamine and MK–801 data

Scopolamine data			MK–801 data		
Response Pair	F (4,24)	P	Response Pair	F (3,18)	P
Phase II					
1–1	11.45	<0.001	1–1	5.89	0.006
1–1R	3.37	0.025	1–1R	1.79	0.186
1–2	3.15	0.033	1–2	4.82	0.012
1–3	7.16	<0.001	1–3	3.37	0.041
1R–1	3.50	0.022	1R–1	1.05	0.394
1R–1R	0.52	0.724	1R–1R	2.07	0.140
1R–2	1.07	0.394	1R–2	0.70	0.565
1R–3	2.17	0.103	1R–3	3.67	0.032
2–1	0.65	0.634	2–1	1.19	0.343
2–2	2.55	0.066	2–2	1.17	0.349
2–3	2.60	0.062	2–3	4.48	0.016
3–1	2.52	0.068	3–1	1.50	0.247
3–2	0.08	0.986	3–2	0.67	0.581
3–3	1.91	0.014	3–3	0.82	0.499
Response Pair	F (4,20)	P	Response Pair	F (2,12)	P
Phase III					
1–1	5.41	0.004	1–1	0.33	0.725
1–1R	2.07	0.123	1–1R	2.61	0.114
1–2	3.82	0.018	1–2	0.14	0.874
1–3	3.33	0.030	1–3	0.91	0.428
1R–1	2.02	0.130	1R–1	1.46	0.271
1R–1R	0.78	0.552	1R–1R	4.31	0.039
1R–2	0.79	0.547	1R–2	0.17	0.843
1R–3	1.40	0.270	1R–3	0.51	0.614
2–1	3.57	0.024	2–1	0.73	0.500
2–2	3.37	0.029	2–2	0.33	0.728
2–3	1.45	0.256	2–3	1.32	0.304
3–1	0.26	0.898	3–1	1.71	0.221
3–2	1.92	0.146	3–2	2.08	0.168
3–3	1.94	0.143	3–3	3.05	0.085

pronounced in magnitude than that produced by scopolamine [$F(4,28)=9.48$, $P=0.0001$]. The 0.2 and 0.3 mg/kg doses significantly differed from saline ($P=0.015$, $P=0.0002$, respectively). No significant differences were observed between saline and either the 0.05 mg/kg dose ($P>0.999$) or the 0.1 mg/kg dose ($P=0.488$). MK–801 imposed a dual effect upon response rate [$F(4,28)=21.72$, $P<0.0001$], with a peak rate increase obtained at 0.1 mg/kg before falling at the highest dose. The quadratic component of this analysis was significant [$F(1,7)=78.87$, $P<0.0001$] (see Fig. 4B).

Like scopolamine, MK–801 administration, particularly at 0.3 mg/kg, increased the amount of cold lever responding occurring at various intervals since the previous reinforcement delivery (Fig. 5B; RMANOVA dose × post-reinforcement interval in 25 s blocks; main effect of MK–801 dose excluding 0.3 mg/kg dose due to insufficient data, [$F(3,18)=6.84$, $P=0.0028$]. For example, when 60 s had passed since the last reinforcer delivery, cold lever responses made up approximately 18% of responses during saline sessions. After administration of 0.3 mg/kg MK–801, cold lever sampling had reached approximately 45%. This 27% difference was maintained until nearly 2.5 min had elapsed since the last reinforcer. Figure 5B also indicates that, under saline conditions during the MK–801 series, cold lever responding 180 s post-reinforcement occurred approximately 50% of the time. This is a much lower percentage than occurred during the scopolamine series (80%). As no-injection sessions were always run following any drug session (with such data excluded from all analyses) to minimize drug carry over effects, the explanation of this difference may lie in the amount of time between the scopolamine and MK–801 sessions. The additional exposure to the paradigm before MK–801 sessions were conducted may have resulted in decreased sampling under certain conditions.

Phase II responding. Given the decline in overall accuracy, response pairs were analyzed as previously described to determine the nature of the impairment. Panels D–F of Fig. 6 show the mean changes in response pairs in relation to MK–801 dose during phase II. MK–801 caused a slight but significant decline in the proportion of 1–1 response pairs (panel D of Fig. 7), decreasing from 92% to 86% (at 0.2 mg/kg) of response pairs beginning with "1". This decline accelerated sharply at 0.3 mg/kg to approximately 75%, though this dose was not included in the statistical analyses for reasons of restricted sample size (see Methods). The decrease in hot lever responding was offset by increased sampling on the other two levers. As was the case with scopolamine, the biggest increase was in the number of 1–3 response pairs, in which the subject returned to the previously hot lever. The percentage of these response pairs increased from about 2.5% to approximately 11% of the total.

Following a reinforcement (panel E of Fig. 6), MK–801 caused a significant increase in the number of 1R–3 response pairs, from 3% to approximately 12% at 0.2 mg/kg, indicating an increased tendency to return to the previously hot lever. Although not included in the statistical analyses, these effects were magnified at 0.3 mg/kg, where a large drop in 1R–1 responding (80% to 30% with an n of 3; panel E of Fig. 6) and an offsetting increase in 1R–1R responding occurred. This effect is most probably derived from the significant decrease in response rate at that dose level, which allowed the RI30 to expire so that the next hot lever response provided a reinforcer. In addition, at the 0.3 mg/kg dose, 1R–3 responding, i.e. returning to the previously hot lever, had increased to almost 30% of total responses.

Following a response on either cold lever (panel F of Fig. 6), MK–801 did not cause any systematic changes in response patterning. There was no dose-dependent increase in perseveration on the previously hot lever (3–3), nor was there an effect upon the rats' tendencies to return to the hot lever following a cold lever response (2–1 or 3–1). At the highest dose, which could not be included in the statistical analysis, a decrease in the number of cold lever perseverative responses (2–2) was accompanied by an increase exceeding that found in the

analysis of doses up to 0.2 mg/kg, in returns to the previously hot lever (2–3).

Phase III responding. Very little effect of MK–801 on response patterning was noted during phase III (panels D–F of Fig. 7). This was, to a large extent, due to the marked decreases in rates of responding at the highest doses. The only statistically significant finding was a slight decrease in the proportion of 1R–1R response pairs. Examination of data from animals that emitted an adequate number of response pairs at the 0.2 mg/kg dose suggested a decline in an incorrect cold lever response being followed by a hot lever response (2–1) and, instead, a propensity to perseverate on the lever which was hot in phase I (2–2) which increased from about 59% to 80%. However, the variability of this effect negated its statistical significance. At the 0.3 mg/kg dose of MK–801, no rats reached the phase III transition.

Discussion

Cholinergic antagonists such as scopolamine and NMDA receptor antagonists such as MK–801 have been shown to impair accuracy in learning and discrimination performance under several different conditions. Scopolamine, for example, has been reported to impair both reversal learning (Soffie and Lamberty 1987) and discrimination learning (Cleeves and Green 1982; Tsai 1987). MK–801 was recently shown to disrupt acquisition of a radial arm maze (Ward et al. 1990) and performance in a spatial learning paradigm (Wozniak et al. 1990). These studies, along with others, clearly indicate the involvement of both cholinergic and NMDA neurotransmitter systems in learning processes. What is as yet unknown, is whether the nature of the learning impairment produced by these two systems is, in fact, the same. The present study sought to examine that issue through analyses of the patterns of errors contributing to changes in overall accuracy on two different repeated learning baselines.

Both scopolamine and MK–801 disrupted the acquisition of three member response sequences in the repeated acquisition paradigm. Across the range of doses used in the present studies, the effect of MK–801 in decreasing overall accuracy was of greater magnitude than the impairment produced in response to scopolamine administration. The behavioral processes underlying these effects, however, i.e. the nature of the errors contributing to the decrements in overall accuracy, differed substantially between the two drugs. Specifically, scopolamine administration was primarily associated with a pattern of errors arbitrarily designated as "skipping", i.e. errors which consisted of proceeding through the three member sequence in an incorrect fashion. Rats skipped from the first to the third member of the sequence, or from the second member back to the first. In contrast, while MK–801 did increase skipping errors to some extent, its predominant effect was to increase what were designated as "perseverative" errors. This consisted of repetitive responding on one member of the sequence (the first or second member) without proceeding on through the sequence.

Previous studies utilizing the repeated acquisition paradigm have proven extremely useful for demonstrating drug effects on learning. This has been particularly true when the repeated acquisition component is alternated with a performance component in a multiple schedule format such that learning and performance effects of a drug can be differentiated. Several CNS compounds have been shown to affect learning in a dose-related manner under these various conditions, including scopolamine. Howard and Pollard (1983) reported increased errors produced by scopolamine on the repeated acquisition of four-response sequences in rats in which light cues signalled completion of each sequence member.

This study, however, appears to be the first to differentiate drug effects on repeated acquisition on the basis of the underlying pattern of errors. Most previous studies have focused only on overall accuracy as a dependent variable which, while useful for documenting a learning deficit, does not allow any delineation of the underlying behavioral processes. Schrot et al. (1981) examined error patterns consisting of either perseverative responses to a single lever or responses in a left-to-right or right-to-left direction (traverses) on a four-response sequence repeated acquisition procedure. These error classes accounted for the majority of errors in the repeated acquisition. In a subsequent study, Schrot and Thomas (1983) found that amphetamine administration increased the percentage of perseverative errors relative to traverse errors. The results reported here extend these types of analyses even further and demonstrate the utility of such efforts for further differentiating drug effects upon repeated acquisition learning.

Both scopolamine and MK–801 administration disrupted acquisition of hot-lever responding in the repeated transition procedure as well. Again, across the range of drug doses used here, MK–801 generally produced a greater decrement in performance. Both drugs produced a dose-related decline in overall accuracy. In addition, both drugs reduced the amount of time rats spent on the hot lever following a reinforcement, with MK–801 producing a stronger effect. For example, at 60 s post-reinforcement, there was a 27% difference in control cold lever sampling versus cold lever sampling following administration of the highest dose of MK–801 while the corresponding effect for the 1.0 mg/kg dose of scopolamine, the dose resulting in the maximal effect at that time point was only 18%.

The behavioral processes underlying the change in overall accuracy were also generally more alike than different for the two drugs on the repeated transition paradigm. In essence, this comparison was restricted to data from phase II results (Fig. 6 and Table 2) since the suppression of responding produced by the highest dose of MK–801 resulted in the failure of any rats to reach phase III at that dose. Thus, the MK–801 dose associated with the maximal impairment of behavior in phase II was unavailable for comparison in phase III. Both scopolamine and MK–801 decreased hot lever responding (1–1) in phase II as the result of increased cold lever responding

(1–2 and 1–3). Scopolamine also decreased hot lever responding following reinforcement delivery, an effect was likewise seen at the 0.3 mg/kg MK–801 dose which was not included in the statistical analyses. One apparent difference between the drugs was that MK–801 administration did increase returns to the previously hot lever under two circumstances in which the effect was not seen with scopolamine: after reinforcement delivery (1R–3) and after a cold lever response (2–3).

It is interesting to note that MK–801 did not increase "perseveration" on the repeated transition procedure, where perseveration was reinforced, as it did on the repeated acquisition procedure. Under the RI schedule in effect during the repeated transition procedure, remaining on the hot lever, i.e. perseveration, was directly reinforced. Thus, where the perseverative type performance produced by MK–801 on the repeated acquisition paradigm might even have been expected to enhance accuracy on the response transition procedure, this was not the case. While the effects of MK–801 may then appear to be inconsistent across the two procedures, they raise alternative interpretations about the similarities and contrasts between the behavioral mechanisms underlying the effects of the two compounds.

Understanding the behavioral mechanism(s) by which a drug acts upon behavior means understanding how the drug affects the factors controlling that behavior, such as its antecedent factors (e.g. deprivation state), current stimulus conditions (e.g. stimulus control) and consequence factors (e.g. the reinforcer). Speculating on a more mechanistic interpretation of the comparative findings on these two repeated learning baselines might include differential alterations in rule-governed behavior, i.e. differential drug effects upon stimulus control of the behavior. In the case of the repeated acquisition paradigm, for example, one could assume that the task involves learning the rule of a three-response sequence without repetition. Scopolamine may be perceived as altering the nature of the rule, that is, how the rat integrates individual components of the sequence, whereas MK–801 may cause forgetting of the basic three lever sequence rule itself (respond once on each lever in a specific order). Such an interpretation would also be consistent with the absence of an enhancing or perseverative effect of MK–801 on the response transition procedure.

While the above explanation may be useful for explaining the absence of any MK–801 enhancement of accuracy on the repeated transition procedure, it does not easily explain the absence of any apparent systematic differences in the error patterns produced by scopolamine and MK–801 in that paradigm. It seems that forgetting the rule itself should produce a different pattern of errors on the repeated transition procedure than forgetting the nature of the rule. In the case of the repeated transition baseline, the rule might best be stated: "perseverate on the hot lever, but increase cold lever sampling as time since the last reinforcer delivery increases". If MK–801 causes forgetting of the rule itself, one might predict it to cause a pattern of more random responding across the three levers. If scopolamine causes forgetting the nature of the rule, one might expect errors such as perseveration on a previously hot lever. However, evidence for a differential pattern of errors was not compelling.

This raises the further possibility that quite different behavioral mechanisms are involved in the effects of scopolamine and MK–801 on these two repeated learning baselines. The fact that both drugs resulted in a shorter post-reinforcement interval to sampling of the cold levers in the presence of differential changes in response rate, leads to the suggestion that both drugs altered temporal processes in the response transition procedure, an effect that was more predominant under these particular contingencies than any changes in rule-governed behavior. Further experiments are quite obviously needed to delineate the exact behavioral mechanisms by which the two compounds caused the various changes observed in these experiments.

Finally, while describing these drug effects as learning impairments, it is important to remember that this study did not provide a mechanism for differentiating learning from performance effects of these drugs. It is conceivable that similar effects might be noted on performance of previously learned behaviors, which could even further change the interpretation of these results.

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