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18. We thank R. Rimas for excellent technical assistance and K. Asin, C. S. Campbell, and H. Koopmans for helpful comments on the manuscript. This work was supported in part by NSF grant BMS 75-17091.

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Methylphenidate in Hyperkinetic Children: Differences in Dose Effects on Learning and Social Behavior

Abstract. *Methylphenidate (Ritalin) is widely prescribed for hyperkinetic children. This study showed a peak enhancement of learning in children after being given a dose of 0.3 milligram per kilogram of body weight, and a decrement in learning in those given larger doses; social behavior showed the most improvement in children given 1.0 milligram per kilogram. These results had been hypothesized from theoretical dose-response curves which indicate different target behaviors would improve at different doses.*

Methylphenidate (Ritalin) is a stimulant drug prescribed extensively to alter the behavior of schoolchildren. There is general agreement that it improves attentional behavior and decreases impulsivity in hyperkinetic children (*1*). Although dose-response curves are usually obtained in animal psychopharmacological research (*2*), there has been little systematic study of dose-response effects of psychoactive drugs on different target behaviors in children (*3*). There have been few attempts to determine whether the optimum dose of methylphenidate for improvement in attention which results in better learning varies from that considered optimum for improvement in social behavior in the classroom. We have postulated theoretical dose-response curves on a milligram per kilogram basis for different target behaviors (*4*), and have theorized from data accumulated from experiments with a more restricted dosage range that low doses of methylphenidate lead to the maximum enhancement of learning performance, whereas much larger doses are required to maximize improvement in social behaviors. The study described herein provided an empirical test of the theorized dose-response curves as measured by target behaviors of learning performance, social behavior, and cardiovascular side effects (*5*).

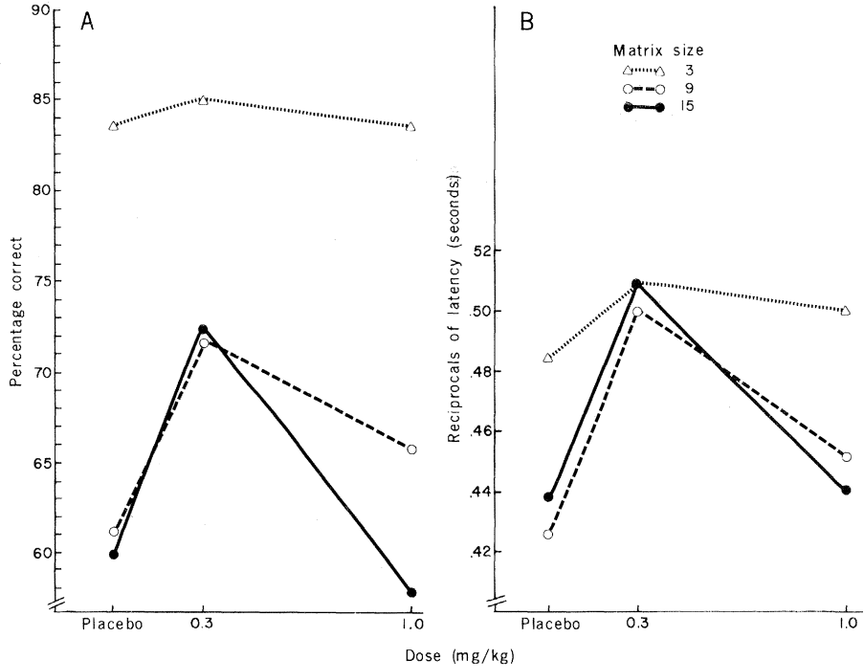

Fig. 1. Dose-response curves for (A) accuracy and (B) latency obtained at differing levels of information load (matrix size) for hyperactive children taking methylphenidate.

All children accepted for our pediatric psychopharmacology project are thoroughly screened. The score they obtain on the Conners' Teacher Rating Scale (*6*) must be 2 standard deviations above the normal mean (*7*, *8*), the pediatric examination must be negative for other major diseases, there must be no indications of serious family pathology on the basis of their social history, and the parents must give their written informed consent. These studies always involve a crossover design with placebo control, strict double-blind conditions, and measures from several behavioral and physiological domains. The capsules (which conceal the contents) containing the methylphenidate tablets are packaged by the pharmacist and then placed in dated envelopes to ensure that the parent actually administers the assigned dosage at the proper time. Additional experimental procedures are described elsewhere (*3*, *9*).

Numerous measures of learning, social behavior, cardiovascular functioning, and psychophysiological function are taken during an intensive 9-week study period. Only the learning, social behavior, and heart rate measures will be described here. The test of short-term memory requires the child to look briefly at a matrix of children's pictures, then respond a few seconds later to a test picture, and indicate whether the test picture was presented previously or not (*3*, *4*). Different numbers of pictures (3, 9, and 15) were included in the presentation matrix; the larger number of pictures increases the information load. Accuracy of recognition, latency of responding to the test pictures, and amount of wiggling on a stabilimetric cushion (*10*) were automatically recorded. The learning performance task was given at the end of each 3-week dosage period 1.5 hours after oral administration of the dose the child had been taking for that period. At the end of each school week the child's classroom teacher completed an Abbreviated Conners' Rating Scale (*11*). We consider this scale to be a measure of the problematical social behavior of the child in the classroom. When the child came to the laboratory for the learning task, the research pediatrician (E.K.S.), about 1.5 hours after the child ingested the capsule, recorded the heart rate after the child had rested for 5 minutes (*5*). Heart rate was obtained with a stethoscope placed over the precordium and was measured for 1 minute with the child seated. Three dosages of methyl-

phenidate were given for 3 weeks each with the sequence of dosages randomized over subjects: placebo, 0.3 mg/kg, and 1.0 mg/kg.

Twenty hyperactive children (18 males and 2 females) participated in the study. The basic demographic data for these subjects are: 18 white, 2 black; mean age, 8.3 years; mean IQ, 99.2; mean Hollingshead social economic status, 4.8 (*12*); mean grade placement, 3.7; and mean initial Conners Abbreviated Rating Scale score, 22.3 (*13*).

The results on the learning test are shown in Fig. 1. An analysis of variance of the accuracy data (Fig. 1A) showed that both dosage ($F = 5.02$; d.f. = 2, 38; $P < .01$) and matrix size ($F = 69.27$; d.f. = 2, 38; $P < .00001$) were statistically significant. Further analyses of variance were computed to isolate the source of significance for information load or matrix size; neither matrix 3 nor matrix 9 was significant, but matrix 15 was ($F = 5.47$; d.f. = 2, 38; $P < .008$). It should be noted that a large number of measures were obtained on this learning task; in Fig. 1 each point on each curve represents a mean of 240 measures.

Figure 1B shows the reciprocal of the mean latency in seconds. This transformation was done simply to plot the latency curves in the same manner as the accuracy curves rather than as an inverted function which would be true if raw latencies were reported. An analysis of variance of the latency data for the correct responses in seconds was calculated, and both dosage ($F = 3.76$; d.f. = 2, 38; $P < .03$) and matrix size ($F = 4.43$; d.f. = 2, 38; $P < .02$) were significant. Further analyses of variance were done to isolate the source of significance; matrix 3 was not significant, matrix 15 ($F = 2.59$; d.f. = 2, 38; $P < .10$) approached significance, and matrix 9 ($F = 3.47$; d.f. = 2, 38; $P < .05$) was significant. Of the above two sets of analyses, we place more emphasis on the dose-response curves for accuracy since accuracy has always produced statistically significant results in previous studies (*14*), whereas the latency data have not proven as reliable over repeated experiments.

The curves for both accuracy and latency in Fig. 1 are remarkably similar to the theoretical dose-response curves previously postulated (*3, 4*). If one considers learning of the hyperactive child to be an important variable, it is apparent from these families of curves that a low dose (0.3 mg/kg) is better in terms of learning and speed of response than a higher dose (1.0 mg/kg). The analyses of

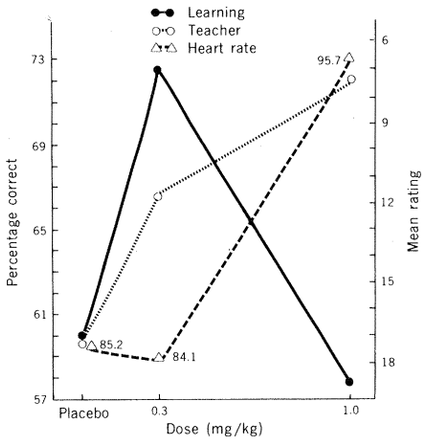

Fig. 2. Three different target behaviors produced three different dose-response curves. The learning curve is the same as the accuracy curve from matrix 15 (Fig. 1), the teacher curve represents social behavior as rated by the teacher, who used a scale on which the numbers become smaller as the child improves, and the heart rate curve (means placed on data points) indicates the number of beats per minute.

information load on the child (matrix size) showed that the largest matrix (accuracy data) carried the statistical significance. In other words, when the task is quite easy, as is in the case with matrix 3, differing dosages have no effect on learning, but when the task becomes difficult, as is presumed to be true of much of the academic material in school, dosage has a definite effect.

Accuracy of performance at a low dose (0.3 mg/kg) is markedly enhanced, but performance deteriorates under a high dose (1.0 mg/kg) and even falls somewhat below the level of performance under placebo. Our theoretical dose-response curves predict learning performance deterioration under higher doses (*3, 4*). Doses larger than 1.0 mg/kg were not included in this study.

Another curve emerges if a different target behavior is examined, namely, the social behavior of the child as rated by the teacher in the classroom. In Fig. 2 we present the mean ratings of the teacher, heart rate, and the curve from matrix 15 for accuracy on the learning task. Each point on the teacher rating curve represents a mean of 540 teacher judgments. Both teacher ratings ($F = 42.39$; d.f. = 2, 34; $P < .00001$) and heart rate ($F = 5.91$; d.f. = 2, 28; $P < .007$) are highly significant. It is clear from Fig. 2 that different target behaviors result in different dose-response curves. Whereas learning performance shows a peak enhancement at a dosage of 0.3 mg/kg, the social behavior shows maximum improvement at 1.0 mg/kg. When the common side effect of tachycardia (*5*) is examined, a somewhat different picture emerges with little or no increase in heart rate at 0.3 mg/kg but a substantial increase at 1.0 mg/kg.

When the amount of wiggling on the stabilimetric cushion is examined, a result similar to that of teacher ratings is obtained. Wiggling decreases significantly as dosage is increased ($F = 4.04$; d.f. = 2, 38; $P < .03$); the recorded movements of the children during the test session were 76.1 with placebo, 50.6 with 0.3 mg/kg, and 38.1 with 1.0 mg/kg.

The data in Figs. 1 and 2 are averaged measures. To be certain the results were not averaging artifacts, we calculated the percentages of children showing their optimum score at each dose level on accuracy on the learning test, teacher rating, and heart rate. These percentages, for placebo and doses of 0.3 mg/kg and 1.0 mg/kg, were, respectively: learning test 10, 65, and 25; teacher rating 0, 28, and 72; and heart rate 30, 13, 57. Sixty-five percent of the children showed their greatest enhancement in performance on the learning test when given the 0.3 mg/kg, as shown in Fig. 1. Therefore, whether the data are analyzed parametrically or by the percentage who demonstrate optimum performance on each drug condition, different dose-response effects are shown for different target behaviors.

Our data have implications for both pediatric psychopharmacology research and the clinical practice of treating hyperactive children. The pediatric psychopharmacologic literature on hyperactivity (*15*) indicates that there have been very few systematic investigations of the effects of dosage on different target behaviors. About 600,000 children in the United States receive stimulant treatment during any one year, although the percentage of school children receiving psychotropic medication is quite small—probably 1.7 to 1.8 percent (*16*). Physicians typically use the titration method (*4*) of increasing dosage until an acceptable report is obtained from the mother about the child's behavior. This traditional practice is followed even though it has been shown (*17*) that parents are insensitive to dose effects and, in fact, on the average, cannot distinguish between placebo and medication. The physician needs to balance the improvement in learning performance against the less than optimal social behavior for each individual case. He should not depend entirely on information from one source or utilize only feedback from one target behavior.

There is evidence that similar dose re-

sponse effects are obtained with drugs other than the stimulants; for example, antidepressants (*18*) and anticonvulsants (*19*) improved attending behavior as the dose was lowered. Although we found a significant decrement in learning in children given 1 mg of methylphenidate per kilogram, a standard medical textbook (*20*) recommends 2 mg/kg as the optimum dose and many writers argue for larger doses (*21*). Our data indicate that dosage should be routinely considered, if not directly manipulated, in pediatric psychopharmacological studies.

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13. On the basis of data collected on 291 normal children and 64 children diagnosed as hyperactive in Champaign-Urbana, Ill. (*7*), a score of 15 out of a possible 30 on the Conners' Abbreviated Rating Scale is two standard deviations above the mean (0.43) for the normal children. Thus, a score of 15 has been set as a minimum cutoff score for accepting children in the project.
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Masking of Electrical by Acoustic Stimuli: Behavioral Evidence for Tonotopic Organization

Abstract. *When pure-tone acoustic masking stimuli of various frequencies were presented simultaneously with electrical stimuli applied to cochlear nucleus, only those maskers within a limited frequency range interfered with the detection of the electrical stimuli. The form of the masking functions obtained suggests that the electrical stimulus directly activated only a small population of neurons which were functioning in a tonotopic fashion.*

Single-unit data from both anesthetized and decerebrate preparations indicate that the neurons of the cochlear nucleus are systematically arranged according to the acoustic frequencies to which they are most sensitive (*1*, *2*). The purpose of the present research was to determine whether the tonotopic organization of the neurons in the cochlear nucleus could also be demonstrated in the unanesthetized, intact animal.

An electrical stimulus delivered within the superior olivary complex can be masked by a simultaneous presentation of an acoustic stimulus (*3*). In our work reported here, we used the masking paradigm to investigate the neural organization of the cochlear nucleus. The approach was based on the assumption that the masking of an electrical stimulus by an acoustic stimulus would be maximal when the two stimuli activated the same target population of auditory neurons. In a nucleus in which the individual neurons were tonotopically organized, the cluster of neurons activated by a near-threshold electrical stimulus would have a limited range of best frequencies, so that acoustic masking should be maximal when the frequency of the acoustic masker falls within that same limited frequency range (*4*). Our experiments indicate that electrical stimuli presented to the cochlear nucleus are, in fact, masked by a limited range of acoustic frequencies, and suggest that tonotopic organization prevails in the cochlear nucleus during alert, waking behavior.

The subjects of our experiments were three adult cats, with stainless steel (75 μm diameter, 0.5 mm exposed tip) electrodes permanently implanted in the cochlear nucleus. A self-paced operant detection task (*5*) was used to measure the sensitivity of the animals to electrical stimuli applied to the electrodes. Briefly, in the self-paced task, the animal initiated a detection trial by placing a paw in a slot operandum, after which the electrical stimulus was presented, with a variable delay of 1 to 9 seconds. A correct detection, or a paw withdrawal within 1.5 seconds of stimulus onset, was rewarded with blended fish; a false alarm, or a paw withdrawal before stimulus onset, was punished by a 12-second time out. A miss, or failure to withdraw the paw within 1.5 seconds, was neither rewarded nor punished.

To determine detection thresholds (the current level at which there were 50 percent correct detections) for animals working in the self-paced task, we used a titration procedure in which stimulus intensity was adjusted, upward after each miss or downward after each correct detection, in steps of 1 db (*6*). These procedures yielded threshold estimates which decreased only slightly during our experiments (*7*). In the present experiments, mean 50 percent detection thresholds ranged from 13 to 20 μa (22 to 26 db with reference to 1 μa) for the three animals. The stimuli used were constant current cathodal pulses of 0.3 msec duration, presented at 5 hertz for a maximum of four pulses per trial.

In the first experiment, we examined the effect of broad-band noise bursts on the detection threshold for electrical stimuli. The noise bursts (20 hertz to 20 khz; 3-msec rise or fall time; 20-msec duration; loudspeaker source 0.6 m from the cat's head; 75 db sound pressure level with reference to 0.0002 dyne/cm^2 for the continuous noise measured in the vicinity of the cat's head) were presented at 5 hertz throughout each threshold session. The electrical stimulation pulses were delivered either 12.6 msec after noise pulse onset (masked condition), in the middle of the interval between noise