Pharmacology Biochemistry & Behavior, Vol 16, pp 423–427, 1982 Printed in the U S A

A Comparison of the Central and Peripheral Effects of Atropine on Force Lever Performance[1]

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Received 16 July 1981

PRESTON, K L AND C R SCHUSTER *A comparison of the central and peripheral effects of atropine on force lever performance* PHARMAC BIOCHEM BEHAV **16**(3) 423–427, 1982 —The central and peripheral effects of atropine, a muscarinic antagonist, on motor control were tested in a force lever apparatus Three rhesus monkeys were trained to extend their arms through a tube and press a manipulandum with between 25 and 40 grams of force for 3 continuous seconds Responding was maintained by the delivery of 1 5 ml of water Single injections of atropine sulfate or atropine methylnitrate (a quaternary derivative of atropine which does not cross the blood brain barrier) were given 30 min prior to the session Atropine sulfate disrupted force lever performance in a dose related fashion Atropine methylnitrate had little or no effect on responding The effects of atropine on motor control as measured in this procedure, therefore, appear to be centrally mediated

Atropine sulfate Atropine methylnitrate Force lever Rhesus monkeys

MANY drugs acting on the nervous system are reported to produce tremor and disturbances of motor control The effects of cholinergic agents on motor control are especially interesting in light of the various motor diseases known to be linked to the cholinergic nervous system Myasthenia gravis, a disease of the peripheral cholinergic system, Parkinson's disease, which can be treated with l-dopa or cholinergic antagonists, and Huntington's chorea, a disease in which improvement has been seen after the administration of agents which raise brain acetylcholine levels, are examples of such diseases [1, 2, 7, 8]

A quantitative method for studying discriminative motor control in unrestrained rats was developed by Falk and Haas [4] and shown to be sensitive to a variety of psychotropic drugs [3] Johanson *et al* [6] who modified this procedure for use with primates were able to demonstrate subtle changes in motor function produced by the administration of acute doses of methamphetamine

The present study was designed to determine the effects of atropine, a muscarinic antagonist, on motor control as measured by this force lever method and to determine whether the effects of atropine were due primarily to its central actions or to more generalized effects on both the central and peripheral nervous system This was accomplished by comparing the effects of atropine sulfate to the effects of atropine methylnitrate Atropine methylnitrate is a quaternary muscarinic receptor blocker which is equipotent to atropine sulfate peripherally [5] but, because it does not readily cross the blood brain barrier, is much less potent centrally Results showed that atropine sulfate had a profound effect on force lever performance while atropine methylnitrate had little or no effect, indicating that atropine's effects on this measure of motor control are centrally mediated

METHOD

Animals

The subjects were one male and two female adult rhesus monkeys weighing between 4 and 8 kg at the beginning of the study One monkey, 9041, was experimentally naive Monkeys 5126 and 6056 had previous lever pressing experience with responding maintained by intravenous drugs and shock

[1]Supported in part by USPHS NIDA Grants No DA00250 and DA00085 (C R Schuster, Principal Investigator) Kenzie L Preston is supported by PHS5-T32 GM-07151 from the National Institute of General Medical Health

TABLE 1
PERFORMANCE INDICES

Efficiency*	=	$\frac{\text{Number of Reinforcers Delivered} \times \text{Minimum Time Requirement (3 sec)}}{\text{In Band Responding Time (sec)}}$
Tonic Accuracy*	=	$\frac{\text{In Band Responding Time (sec)}}{\text{Total Responding Time (sec)}}$
Work Rate	=	$\frac{\text{Total Responding Time (sec)}}{\text{Session Time (sec)}}$
Mean Band Entrances*	=	$\frac{\text{Total Band Entrances}}{\text{Number of reinforcers delivered}}$
Mean In Band Time*	=	$\frac{\text{In Band Responding Time (sec)}}{\text{Total Band Entrances}}$
Reinforcers	=	Number of Reinforcers Delivered Within 30 Minutes (Maximum of 50)

*If responding is completely eliminated by any manipulation, this index cannot be calculated

punishment experience but had not received any drug nor were in any experiment for one year prior to this experiment Each monkey was housed individually in a standard metal cage The colony room temperature was 21±1°C

Each monkey received a total of 175 to 225 ml of water daily (75 ml maximum during the session, the rest given in the home cage after the daily session and titrated to the animal's needs to avoid dehydration while still maintaining responding for water delivery) The monkeys received free access to Purina Monkey Chow and two sugar cubes saturated with liquid vitamins (Vitol, Vet-A-Mix, Inc , Sanandoah, IA) daily in the home cage

Apparatus

The force lever system is the same as that described by Johanson *et al* [6] and is a modified version of an apparatus described by Falk and Haas [4] designed to monitor discriminative motor control in rats

The apparatus consisted of a standard metal cage which had one side removed so that the monkey could place its arm through an adjustable Plexiglas tube and press on a conical shaped manipulandum (maximum displacement 0 1 mm) located at the end of the tube and attached to a force transducer This apparatus was situated in two sound attenuating wooden boxes, one housing the animal chamber and one housing the Plexiglas tube, manipulandum, and force transducer A Plexiglas wall separated the two chambers A water cup was located on the Plexiglas wall to the left of the Plexiglas tube and was attached by plastic tubing to a peristaltic infusion pump (7540X, Cole-Parmer Instrument Co , Chicago, IL) located outside the wooden boxes Four amber indicator lights were located to the left of the water cup on the Plexiglas wall in a verticle arrangement The amount of force applied to the manipulandum was monitored by a Statham force transducer (Model UC3, Statham Instruments, Oxnard, CA), a Beckman Dynograph (Type R411, Beckman Instruments, Inc , Lincolnwood IL) and BRS/LVE solid-state programming and recording equipment (BRS/LVE, Beltsville, MD) Calibration of the apparatus was checked regularly by suspending weights from the manipulandum

Terminal Schedule

The monkey was required to extend its arm through the Plexiglas tube and press on the lever with a force greater than 25 grams and less than 40 grams for 3 continuous seconds If the force exerted was outside these limits (less than 25 grams or greater than 40 grams) for more than 30 milliseconds, the time requirement reset When a trial was successfully completed (i e , the 3 second requirement was met), the pump delivered 1 5 ml of water During water delivery, all lights were extinguished in the cubicle, and responding had no programmed consequences A session ended after 50 completed trials, or after 30 minutes had elapsed, whichever came first

Indicator lights provided feedback for responding One of three lights was lit when the pressure on the lever was between 10 and 25 grams, 25 and 40 grams, or above 40 grams, respectively A light located above the indicator lights in the experimental chamber indicated when the session was on

Total session time and time spent responding between 10 and 25 grams (below band), between 25 and 40 grams (in band), and above 40 grams (above band) were recorded on four timers Counters recorded the number of times the response force entered the required band width (from either above or below band) and the number of water deliveries obtained within the 30 minute time limit Total time responding was calculated by summing the times recorded for below, in, and above band responding

Data Analysis

Using the above measures, the indices in Table 1 were calculated for each experimental session These indices have previously been shown by Falk [3] and Johanson *et al* [6] to be sensitive to the effects of various psychotropic drugs

Efficiency, tonic accuracy, and work rate are relatively independent and vary between 0 and 1 0 with higher values

corresponding to better performance Efficiency is a measure of how well the monkey performed relative to a perfect score but independent of the number of reinforcers it earned, that is, it is the time spent pressing the lever with between 25 and 40 grams of force relative to the minimum in band time required to earn a given number of reinforcers Tonic accuracy is a measure of how much time the monkey spent responding within the 25 to 40 gram range relative to the total amount of time it spent pressing the lever with 10 or more grams of pressure Work rate measures the amount of time the monkey spent pressing the lever with 10 or more grams of pressure relative to the time it spent engaging in other behaviors While work rate is not a measure of motor control, it is a good measure of general performance Mean band entrances is the average number of band entrances made per reinforcer earned A drug which caused a tremor would be expected to increase mean band entrances Mean in band time gives the average length of time spent responding in the required band width per band entrance Although these last two indices are related, the effects of some drugs could differentially affect the two scores For example, a drug which caused a gradual drift in the force exerted on the lever could result in an increase in the in band time without increasing to as large an extent the total number of band entrances

Experiment

When responding became stable, single injections of atropine sulfate (Aldrich) or atropine methylnitrate (Sigma) were given intramuscularly 30 minutes prior to the experimental session in doses ranging from 0 025 to 1 6 mg/kg of the salt For an equal number of mg of atropine sulfate and atropine methylnitrate, 5% more atropine base moeties were delivered with the atropine methylnitrate administration These doses were given in 0 1 ml/kg of physiological saline in ascending order, with all doses of atropine sulfate being given first Drug was given no more often than every fourth session and only after responding returned to baseline Saline injections were given IM one or two sessions prior to each drug session and served as control

RESULTS

Figure 1 shows the dose response curves of the two drugs for each monkey In each subject, the effects of atropine sulfate were dose dependent, such that efficiency, tonic accuracy, work rate, mean in band time, and number of reinforcers earned all decreased with increasing doses while mean band entrances per reinforcer increased with increasing doses of drug Responding was totally disrupted by a dose of 0 8 mg/kg of atropine sulfate in two subjects (5126 and 6056) and by a dose of 0 2 mg/kg in subject 9041

At most doses, atropine methylnitrate showed little or no effect on the measured indices (Fig 1) A dose of atropine methylnitrate which supplied twice as many moles of atropine as the highest dose of atropine sulfate had only negligible effects on the responding of subjects 5126 and 6056 In subject 9041, responding was disrupted by the highest dose of atropine methylnitrate resulting in 40% of possible reinforcers being earned and a decrease in work rate, but there were no increases in mean band entrances or other measures to suggest that this was a specific effect on motor function

Figure 2 shows representative Beckman analog recordings of responding by subject 5126 after the administration of saline, 0 8 mg/kg of atropine sulfate, or 0 8 or 1 6 mg/kg of

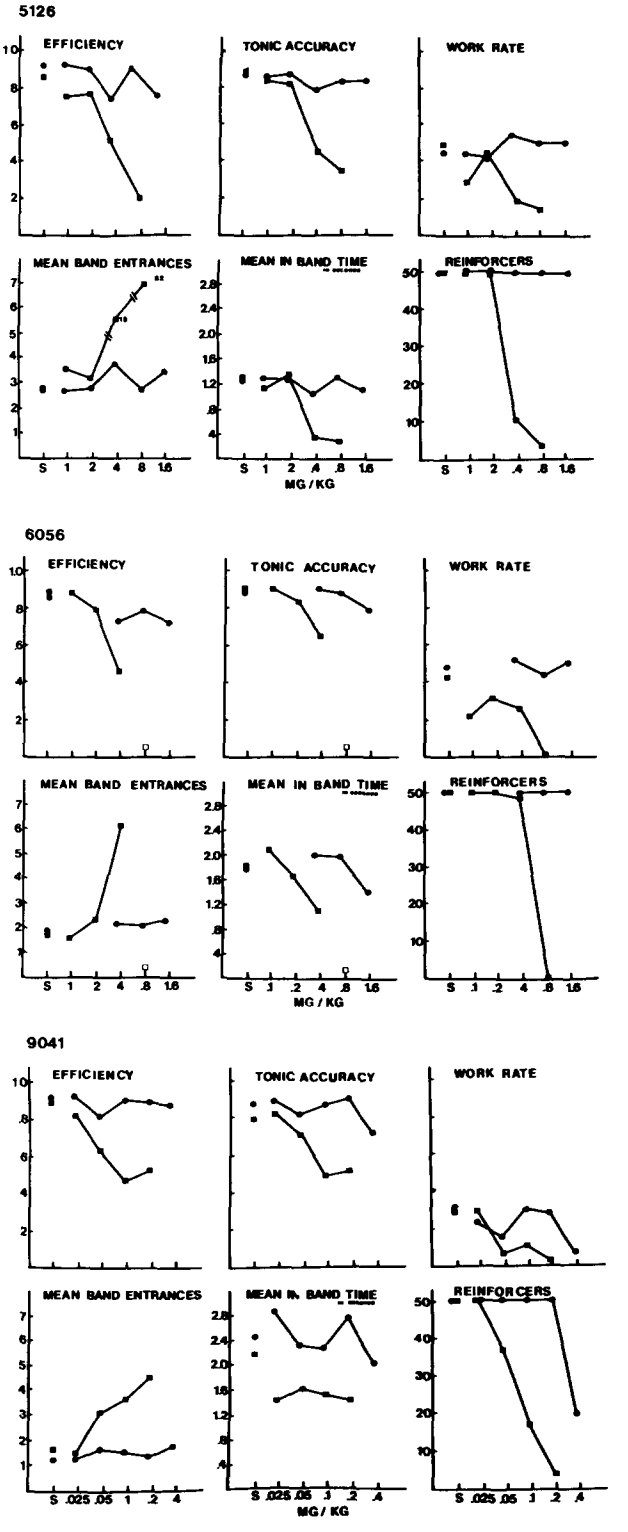

FIG 1 The effects of single injections of atropine sulfate (squares) and atropine methylnitrate (circles) on the six performance indices of three subjects See Table 1 for description of the performance indices

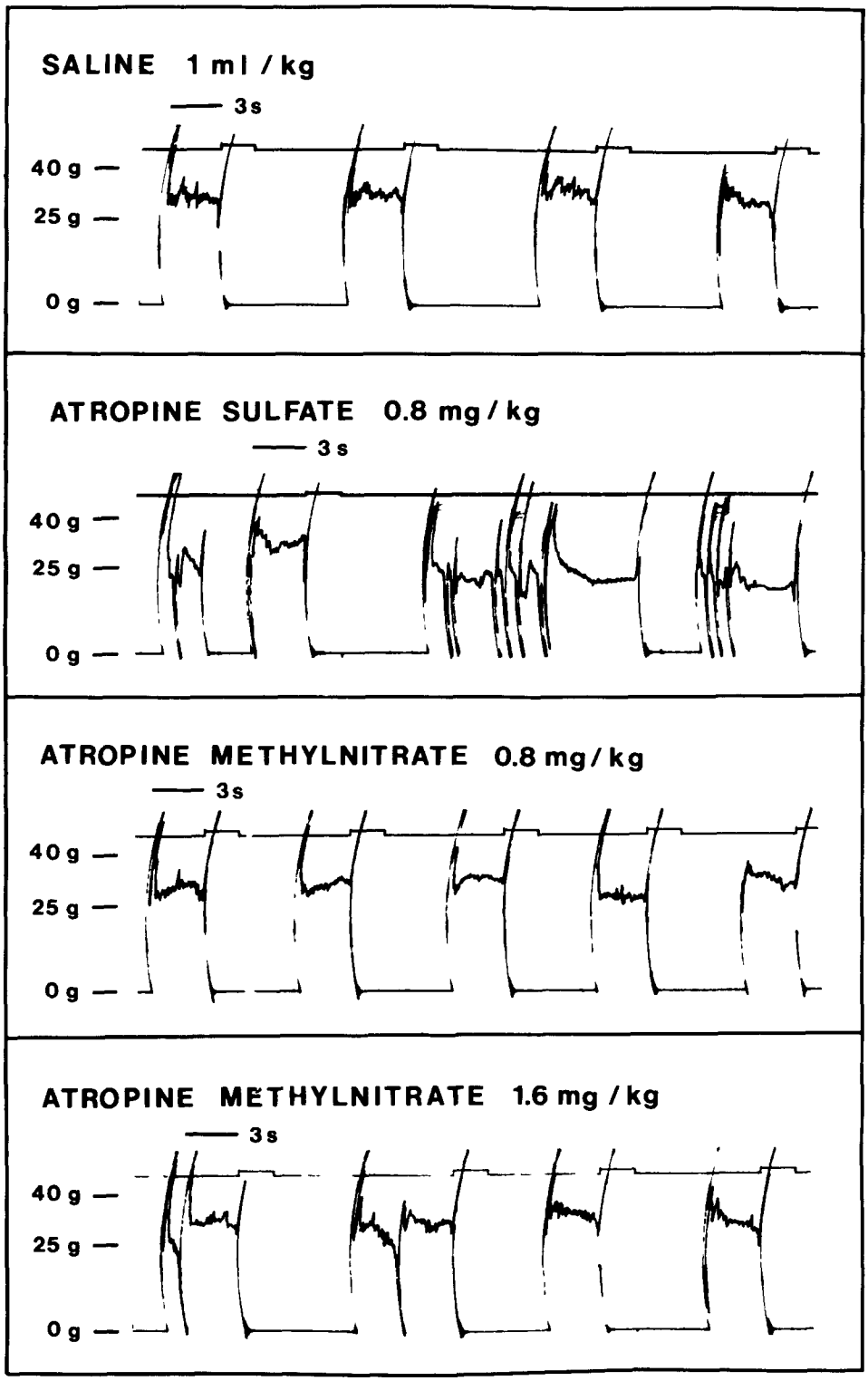

FIG 2 Analog recordings of responding of subject 5126 after the IM administration of saline, atropine sulfate 0 8 mg/kg, or atropine methylnitrate 0 8 or 1 6 mg/kg The tracing moves horizontally with time and vertically with changes in force exerted on the lever The notches in the line at the top of each recording indicate delivery of water

atropine methylnitrate Performance in the presence of saline shows the typical pattern of baseline responding The topography of responding differed somewhat between monkeys and accounted for individual differences in baseline scores Performance in the presence of 0 8 mg/kg of atropine methylnitrate resembles that of saline whereas performance in the presence of 0 8 mg/kg of atropine sulfate shows many band entrances and reduced time in band, resulting in a substantial reduction in number of water deliveries At the dose of 1 6 mg/kg, the tracing shows that the monkey had difficulty holding the lever for the required 3 seconds, although the basic pattern of the response tracing is essentially normal

DISCUSSION

The result show that atropine has profound effects on force lever performance when it is administered in a form which readily enters the central nervous system (atropine sulfate) All performance indices indicated a decline in motor control with increasing doses of atropine sulfate The increases in mean band entrances indicate the presence of tremor in the atropine sulfate treated subjects while decreases in tonic accuracy show a decreased ability to hold the lever in band for the required time This is in contrast to the effects of methamphetamine, as seen by Johanson *et al* [6], which produced increases in band entrances without affecting efficiency or tonic accuracy

The administration of atropine in a form which did not readily cross the blood brain barrier (atropine methylnitrate) was far less effective in disrupting performance than atropine sulfate Even a dose of 1 6 mg/kg of atropine methylnitrate, which delivered twice the number of atropine moeties necessary to totally disrupt behavior when administered in the sulfate form, had minimal effects on responding Since atropine methylnitrate has been shown to be equipotent to atropine sulfate peripherally, it can be concluded that the effects of atropine on force lever performance are primarily centrally mediated

ACKNOWLEDGEMENTS

The authors would like to express their appreciation to Dr Thomas Aigner for his technical and procedural advice Portions of these data were presented at the 1981 convention of the Association for Behavior Analysis

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