BEHAVIORAL AND PHARMACOLOGICAL MODULATION OF RESPIRATION IN RHESUS MONKEYS

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Changes in respiration associated with schedule-controlled behavior were determined in seated rhesus monkeys prepared with a pressure-displacement head plethysmograph for monitoring ventilation continuously during behavioral experiments. Subjects were trained to press a lever under fixed-ratio 40 and fixed-interval 300-s schedules of stimulus termination. Episodic increases in ventilation were closely associated with periods of responding under both schedules. Recurring episodes of increased ventilation occurred during fixed-ratio responding, and were separated by brief 10-s timeouts during which ventilation decreased. Under the fixed-interval schedule, both ventilation and response rate typically increased as the 300-s interval elapsed. The effects of cocaine, caffeine, and two adenosine agonists, 5'-N-ethylcarboxamidadenosine (NECA) and 2-(carboxyethylphenylamino)adenosine-5'-carboxamide (CGS 21680), on behavior and respiration were determined using a cumulative-dosing procedure. Drug-induced suppression of behavior eliminated the episodic increases in ventilation during the performance components of both schedules. Schedule-related increases in ventilation were compared to those produced by elevated levels of CO₂ in inspired air. Exposure to 4% CO₂ mixed in air increased ventilation in all subjects, and the combined effects of CO₂ exposure and schedule-controlled responding on respiration appeared to be additive. The results suggest that behavioral activities may increase ventilation through increased metabolic demand and increased CO₂ production.

Key words: respiration, caffeine, cocaine, adenosine, fixed-interval schedule, fixed-ratio schedule, stimulus-termination schedule, plethysmograph, lever press, rhesus monkey

The influence of operant conditioning on physiological systems has been studied actively within the framework of two general experimental approaches. One approach, referred to as a contingent model (Brady & Harris, 1977), has emphasized environmental and behavioral interactions that occur as a consequence of significant physiological changes (i.e., a specified physiological response is treated as an operant). Most studies have used either heart rate or blood pressure as the operant and have focused on the role of behavioral influences in the etiology of hypertension (Benson, Herd, Morse, & Kelleher, 1969; Benson, Shapiro, Tursky, & Schwartz, 1971; Engel & Schneiderman, 1984; Harris, Gilliam, Findley, & Brady, 1973; Talan & Engel, 1986). The other approach, referred to as a concurrent model

(Brady & Harris, 1977), has emphasized concomitant physiological changes associated with environmental and behavioral interactions. The cardiovascular (Forsyth, 1969; Herd, Morse, Kelleher, & Jones, 1969; Kelleher, Morse, & Herd, 1972) and endocrine (Mason et al., 1968) systems have been the major focus of traditional concurrent models, although some attention has also been focused on the central nervous system (Halas, Beardsley, & Sandlie, 1970; Saunders, 1971; Smith, Astley, Hohimer, & Stephenson, 1980) and gastrointestinal function (Ader, 1971). Reliable quantitative relationships between behavior and transient physiological changes have been well documented using a variety of nonhuman animal species and conditioning procedures (Brady & Harris, 1977).

Considerable effort has been directed toward defining mechanisms that mediate changes in physiological processes associated with behavior. Episodic changes in heart rate and blood pressure are frequently confined to experimental periods during which subjects are engaged in some schedule-controlled performance, suggesting that skeletal muscle activity may directly influence cardiovascular activity. Squirrel monkeys trained to respond under fixed-ratio (FR) and fixed-interval (FI) schedules of stimulus termination developed in-

This research was supported by U.S. Public Health Service Grants DA-05346, DA-01161, DA-06264, and RR-00165 (National Center for Research Resources, National Institutes of Health). The Yerkes Regional Primate Research Center is fully accredited by the American Association for Accreditation of Laboratory Animal Care. The authors gratefully acknowledge the technical assistance of A. M. McDonough, P. M. Plant, and F. H. Kiernan, the participation of J. L. Grover, and the constructive reading of the manuscript by L. D. Byrd and K. F. Schama. Reprint requests should be addressed to Leonard L. Howell, Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia 30322.

creases in heart rate and mean arterial blood pressure in association with characteristic patterns of lever pressing, and blood pressure generally corresponded with the rate at which the subjects pressed the response lever (Benson et al., 1969; Herd et al., 1969; Kelleher et al., 1972). Similarly, baboons trained to respond on an FR escape-avoidance procedure for extended periods of observation showed substantial increases in blood pressure during performance intervals within daily experimental sessions (Findley, Brady, Robinson, & Gilliam, 1971). Even when significant physiological changes occur in the absence of behavior directed at the operant manipulandum, mediation of skeletal muscle activity is difficult to exclude. For example, large increases in heart rate and blood pressure have been reported in relatively motionless rhesus monkeys performing forceful, static contraction of skeletal muscle (Dews & Herd, 1974).

Interestingly, respiration has received little attention as a physiological concomitant of operant conditioning and schedule-controlled behavior. The lack of studies on respiration is particularly surprising given the integrated nature of the cardiopulmonary system, and may reflect inadequate methods related to continuous measurement of respiration in behaving animals. The present study describes a method for monitoring ventilation continuously in actively responding nonhuman primates. In seated rhesus monkeys trained to lever press under FR and FI schedules of stimulus termination, ventilation was measured using a pressure-displacement head plethysmograph (Howell, Bergman, & Morse, 1988). The design of the head plethysmograph eliminated nonrespiratory movement artifacts that are frequently obtained with alternative methods and permitted precise control of the content of air or gas inhaled by the subject. Moreover, the technique permitted studies of the behavioral and respiratory effects of selected drugs in subjects with schedule-related elevations in ventilation.

Adenosine and the cyclic nucleotide system appear to be involved in the function of peripheral O_2 -sensitive chemoreceptors and in the control of ventilation by the central nervous system (Griffiths & Holgate, 1990). Metabolically stable analogues of adenosine stimulate respiration in primates ostensibly through activation of peripheral O_2 -sensitive mecha-

nisms (Howell, 1993b). In addition, there is good evidence that antagonism of endogenous adenosine is a predominant mechanism mediating the behavioral-stimulant effects of caffeine and related xanthines (Snyder, Katims, Annau, Bruns, & Daly, 1981). The behavioral-depressant effects of adenosine analogues are attenuated by xanthines in a manner that indicates a competitive pharmacological antagonism (Goldberg, Prada, & Katz, 1985; Logan & Carney, 1984; Spealman, 1988), and the relative potencies of xanthines for increasing rates of schedule-controlled responding in primates correlate with their potencies for attenuating the rate-decreasing effects of the adenosine agonist, 5'-N-ethylcarboxamidadenosine (NECA) (Spealman, 1988). Caffeine and related xanthines also stimulate respiration in primates, but their effects likely involve central CO_2 -sensitive mechanisms and are linked to inhibition of cyclic nucleotide phosphodiesterases (PDE) responsible for the hydrolytic inactivation of cyclic adenosine monophosphate (AMP). For example, caffeine and 3-isobutyl-1-methylxanthine (IBMX) increase ventilation during exposure to elevated levels of CO_2 mixed in air such that the CO_2 response curve is shifted upward in a parallel manner (Howell, 1993a). The additive effects of xanthines and CO_2 observed during hypercapnia are indicative of central respiratory stimulation (Mazzarelli, Jaspar, Zin, Aranda, & Milic-Emili, 1986; Trippenbach, Zinman, & Milic-Emili, 1980). Moreover, Type IV (cAMP-specific, cGMP-insensitive)-selective PDE inhibitors have pronounced respiratory-stimulant effects similar to those of xanthines under conditions of normocapnia and hypercapnia, and the potencies of Type IV-selective inhibitors and several xanthines as respiratory stimulants correspond with their potencies as PDE inhibitors (Howell, 1993a; Howell, Morse, & Spealman, 1990).

Due to the reported involvement of adenosine and the cyclic nucleotide system in respiration and behavior, the present study characterized the behavioral and respiratory effects of caffeine and two adenosine agonists, NECA and CGS 21680. Moreover, the effects of caffeine were compared to those of cocaine, a central nervous system stimulant with biochemical actions that are not believed to involve the cyclic nucleotide system directly (Ritz, Lamb, Goldberg, & Kuhar, 1987; Woolverton

& Kleven, 1988). In addition, schedule-related increases in ventilation were compared to those produced by elevated levels of CO₂ in inspired air to investigate physiological mechanisms that may mediate the observed changes in ventilation associated with schedule-controlled behavior. The results demonstrated a close correspondence between ventilation and the rate of schedule-controlled behavior under all experimental conditions.

METHOD

Subjects

Three adult male (RBL, RJF, and RLM) rhesus monkeys (*Macaca mulatta*) weighing between 8.4 and 13.2 kg served as subjects. Between experimental sessions, subjects lived in individual home cages and were provided daily access to food (Purina® monkey chow, fresh fruit and vegetables) and unrestricted access to water. All were experimentally naive at the beginning of the study.

Apparatus

During experimental sessions, subjects were seated in a primate chair constructed of Plexiglas and enclosed within a ventilated, sound-attenuating chamber. A response panel mounted on the front of the chair was equipped with a response lever (BRS/LVE Model PRL-001) that operated with a required pressure of 50 g (0.5 N) static weight or less. A pair of 5-W colored lights (red and white) were mounted on the top of the panel just above eye level. The subject's tail was held motionless in a small stock, and two brass plates rested on a shaved portion near the end. Electrode paste (EGK Sol) minimized changes in impedance between the tail and the brass plates when a 10-mA electric stimulus of 200 ms duration was delivered. A microcomputer controlled experimental events and recorded and stored data. Responses also were recorded graphically on a cumulative recorder. Ventilation was monitored continuously with a pressure-displacement head plethysmograph, as described previously (Howell et al., 1988). A sealed, rectangular helmet (9.5 cm by 15 cm by 11 cm) made of 1/16-in. Lexan with a hole for the neck was placed over the subject's head and served as a pressure-displacement plethysmograph. A continuous flow (10 L/min) of

air or gas, monitored by a flow meter (Cole-Parmer Model PRO34-FMO34), entered the helmet through a port in front of the subject's face and was extracted by a vacuum pump (Cole-Parmer Model 7530-60) through a port behind the subject's head. A second flow meter monitored the flow (10 L/min) of gas extracted by the pump. Changes in flow within the helmet resulting from inspiration and expiration were measured by a pressure transducer (Micron Instruments Model MP-15) connected to a polygraph (Grass Instruments Model 7D). A polygraph integrator (Grass Instruments Model 7P10F) converted the flow signal to a volume measure. A microcomputer interfaced to the polygraph and to the polygraph integrator analyzed and stored data. Respiratory rate was determined directly by counting changes from positive to negative flow. Minute volume was determined by integration of the pressure-compensated plethysmograph signal after calibrated offset for bias flow, and tidal volume was calculated as the quotient of minute volume and respiratory rate. Continuous white noise and an exhaust fan masked extraneous sounds during all sessions.

Procedure

Fixed-ratio schedule. Subjects were trained to press a response lever under an FR 40 schedule of stimulus termination before the head plethysmograph was introduced to measure ventilation. A red light illuminated the experimental chamber during each FR component, and the subject had 30 s to complete 40 responses and terminate the light that was associated with an impending electric stimulus. When the subject completed 40 responses, a white light was illuminated for 5 s, followed by a 10-s timeout period during which the chamber was darkened and responses had no scheduled consequences. If 30 s elapsed prior to completion of 40 responses, a 10-mA stimulus was delivered once every 10 s until the FR 40 was completed or five presentations of the 10-mA stimulus had occurred; this was followed by a 10-s timeout period. Daily experimental sessions consisted of four sequential components; each component included an extended (10-min) timeout that was followed by a 15-min period during which the FR 40 schedule was in effect. The total session time was approximately 100 min, and sessions were conducted 5 days per week. When schedule-

appropriate patterns of responding developed and rates of responding stabilized, subjects were introduced and adapted to the head plethysmograph. Stable measures of ventilation were obtained over several months before the behavioral and respiratory effects of caffeine, cocaine, NECA, and CGS 21680 were determined in each subject using a cumulative-dosing procedure similar to that described by Kelleher and Goldberg (1979) and Wenger (1980). Typically, a complete dose-effect curve was established during a single session for each drug by injecting (intramuscularly) sequentially higher doses into the thigh or calf muscle. Saline or drugs were injected at the beginning of the extended (10-min) timeout periods.

Fixed-interval schedule. After experiments were completed with the FR schedule, the schedule was changed to an FI 300-s schedule of stimulus termination with a 5-s limited hold. A red light illuminated the experimental chamber during the 300-s interval, and after 300 s elapsed, the subject had 5 s to press the lever and terminate the light that was associated with an impending electric stimulus. When the subject pressed the lever during the limited hold and avoided the 10-mA stimulus, a white light was illuminated for 2 s; it was followed by a 60-s timeout period during which the chamber was darkened and responses had no scheduled consequences. In the absence of a response during the limited hold, an electric stimulus was delivered once, followed by a 60-s timeout. Daily experimental sessions consisted of four sequential components; each component included an extended (10-min) timeout that was followed by three consecutive FIs. The total session time was approximately 112 min, and sessions were conducted 5 days per week. When schedule-appropriate patterns of responding developed and rates of responding stabilized, the behavioral and respiratory effects of caffeine, cocaine, NECA, and CGS 21680 were determined in each subject using a cumulative-dosing procedure.

Fixed-interval schedule and CO₂ exposure. Subsequent experiments exposed subjects to 4% CO₂ mixed in air during FI Components 2 and 4 or during the extended timeout periods preceding FI Components 2 and 4 of the session. In drug experiments, the following arrangement ensured that the time between drug administration and CO₂ exposure was the same for each experimental condition. When sub-

jects were exposed to CO₂ during FI Components 2 and 4, saline or cumulative doses (10 mg/kg and 30 mg/kg) of caffeine were administered at the start of FI Components 1 and 3 of the session. When subjects were exposed to CO₂ during the extended timeout periods preceding FI Components 2 and 4, saline or cumulative doses of caffeine were administered at the start of the extended timeout periods preceding FI Components 1 and 3 of the session.

For all experiments (FR and FI schedules), drugs were administered on Tuesdays and Fridays, and saline (control) was administered on Thursdays. The effects of a full range of doses of each drug were determined at least twice in each subject. To preclude excessive stimulus presentations due to drug-induced impairment of responding, the 10-mA stimulus source was disconnected after the initial stimulus presentation on days when drugs were administered. The subjects seldom received a stimulus presentation when the stimulus unit was connected, and responding was well maintained when the stimulus unit was periodically disconnected.

Data Analysis

Mean ($\pm SD$) control values for response rate, respiratory rate, tidal volume, and minute volume were determined for individual subjects by averaging values obtained during all saline control sessions ($n > 10$) for each experimental condition. Behavioral and respiratory measures were calculated separately for each FR or FI component during the time the red light was present. Representative cumulative records and polygraph recordings were selected by the following criteria. For individual subjects, saline sessions that most closely approximated the mean rate obtained for all administrations of saline were selected. The same criterion applied when a drug dose was administered on three or more occasions; sessions that most closely approximated the mean rate obtained for all administrations of that dose were selected. Data presented in the dose-effect curves were calculated for individual subjects and are presented as the mean for the group.

Drugs

The drugs studied were caffeine (Sigma), 2-(carboxyethylphenylamino)adenosine-5'-

Table 1

Control response rate and ventilation values. Mean ($\pm SD$) response rate, respiratory rate, tidal volume, and minute volume are derived from control (saline) sessions when subjects breathed air only and are based on 10 or more observations in each subject. Response rate was not recorded during timeout periods.

Condition	Subject	Response rate (response/s)	Respiratory rate (breaths/min)	Tidal volume (mL/breath)	Minute volume (L/min)
FR component	RBL	2.1 $\pm$ 0.3	25.7 $\pm$ 3.2	142.5 $\pm$ 45.3	3.7 $\pm$ 1.4
	RJF	5.1 $\pm$ 0.5	49.5 $\pm$ 4.6	97.7 $\pm$ 9.9	4.8 $\pm$ 0.6
	RLM	2.5 $\pm$ 0.5	29.0 $\pm$ 3.1	99.6 $\pm$ 13.4	2.9 $\pm$ 0.5
	Group	3.2 $\pm$ 0.4	34.7 $\pm$ 3.7	113.3 $\pm$ 14.6	3.9 $\pm$ 0.5
FR timeout	RBL	—	20.8 $\pm$ 2.6	121.9 $\pm$ 39.7	2.5 $\pm$ 0.9
	RJF	—	35.7 $\pm$ 3.6	88.6 $\pm$ 20.6	3.2 $\pm$ 0.8
	RLM	—	23.7 $\pm$ 2.0	96.0 $\pm$ 14.9	2.3 $\pm$ 0.5
	Group	—	26.7 $\pm$ 2.7	102.2 $\pm$ 10.1	2.7 $\pm$ 0.3
FI component	RBL	0.6 $\pm$ 0.2	23.9 $\pm$ 2.8	169.9 $\pm$ 31.6	4.1 $\pm$ 0.7
	RJF	1.0 $\pm$ 0.4	41.8 $\pm$ 5.8	143.3 $\pm$ 31.5	6.0 $\pm$ 1.5
	RLM	0.3 $\pm$ 0.1	26.8 $\pm$ 2.1	144.9 $\pm$ 28.2	3.9 $\pm$ 0.6
	Group	0.6 $\pm$ 0.2	30.8 $\pm$ 3.6	152.7 $\pm$ 10.5	4.7 $\pm$ 0.8
FI timeout	RBL	—	20.9 $\pm$ 2.1	153.1 $\pm$ 32.5	3.2 $\pm$ 0.6
	RJF	—	35.5 $\pm$ 3.1	124.1 $\pm$ 27.0	4.4 $\pm$ 0.7
	RLM	—	23.4 $\pm$ 2.1	138.3 $\pm$ 24.2	3.2 $\pm$ 0.5
	Group	—	26.6 $\pm$ 2.4	138.5 $\pm$ 8.4	3.7 $\pm$ 0.4

carboxamide (CGS 21680; Ciba-Geigy), cocaine hydrochloride (National Institute on Drug Abuse), and 5'-N-ethylcarboxamidadenosine (NECA; Research Biochemicals). NECA was dissolved in a small amount of 0.2 N HCl and then diluted with 0.9% saline (pH = 4.5 to 6.0). Caffeine, cocaine, and CGS 21680 were dissolved in 0.9% saline. Injection volumes were 0.5 to 2.0 mL.

RESULTS

Fixed-Ratio Schedule

Responding during the FR 40 schedule was characteristic of performance maintained under FR schedules of stimulus termination in monkeys (Morse & Kelleher, 1966). A brief pause in responding at the beginning of each FR was followed by an abrupt transition to a high rate of responding until the 40 responses were completed. Mean response rates during control (saline) sessions for the individual subjects ranged from 2.1 to 5.1 responses per second (Table 1).

Cumulative records of FR performance in Subject RLM illustrate the pattern of responding typically maintained during control sessions (Figure 1, top) and the effects of caffeine (3.0 to 30.0 mg/kg) administration using a

cumulative-dosing procedure (Figure 1, bottom). Saline administration at the beginning of successive timeouts had no systematic effect on response pattern or rate. Similarly, low doses of caffeine (3.0 to 10.0 mg/kg) had little or no effect on responding. However, the highest dose of caffeine (30.0 mg/kg) markedly disrupted the response pattern and decreased response rate well below control values.

Polygraph tracings of ventilation in subject RBL illustrate changes in respiration associated with FR performance (Figure 2). During control sessions, ventilation typically was uniform and stable during the 10-min extended timeout (Figure 2, top). However, ventilation increased markedly during the 15-min FR component, due primarily to increases in respiratory rate with less pronounced increases in tidal volume (Table 1). Moreover, there were episodic increases in ventilation associated with periods of schedule-controlled responding. Episodes of increased ventilation occurred when the red light was illuminated and the FR schedule was in effect; these episodes were separated by the 5-s reinforcement light and the brief 10-s timeout during which ventilation decreased. Electric stimulus presentation was infrequent and contributed little or nothing to the observed increases in ventilation. In the example shown, a cumulative dose

Fig. 1. Cumulative records of lever pressing in Subject RLM that display the effects of saline administration (top) and cumulative doses of caffeine (bottom) on responding maintained by an FR 40 schedule of stimulus termination. Abscissae: time. Ordinates: cumulative responses. The response pen reset after 500 responses and at the completion of each 15-min FR component. The response pen deflected upon completion of each FR 40. Downward pen deflection on the time axis indicates when electric stimulus presentation was scheduled to occur.

of 10.0 mg/kg caffeine increased ventilation during the extended timeout and during the FR component, but the episodic increases in ventilation associated with schedule-controlled responding were still evident (Figure 2, bottom).

A full range of doses of caffeine and several other drugs with reported behavioral and respiratory effects was characterized in subjects trained to respond under the FR 40 schedule. Each of the drugs produced dose-dependent decreases in mean FR response rate, and the highest dose of each drug markedly suppressed FR responding in all subjects (Figure 3). During control sessions, ventilation was greater during FR components compared to extended timeouts (Table 1). However, as FR response rate decreased due to drug administration, ventilation differed little during FR components and extended timeouts (Figure 3, Table 2). The latter results were obtained with several

drugs that had differential effects on respiration. Caffeine increased tidal volume, whereas cocaine, NECA, and CGS 21680 decreased tidal volume (Table 2). In addition, only caffeine increased respiratory rate and minute volume during the extended timeouts and during FR components (Figure 3A, Table 2). Compared to caffeine, the effects of cocaine, NECA, and CGS 21680 on respiratory frequency and minute volume were less pronounced and dependent on the baseline conditions. Cocaine produced modest increases in respiratory rate and minute volume during the extended timeouts but had little or no effect during FR components. NECA and CGS 21680 also produced modest increases in respiratory rate and minute volume during the extended timeouts but slightly decreased respiratory rate and minute volume during FR components (Figure 3B, C, and D; Table 2). Thus, caffeine-induced increases in respira-

Fig. 2. Polygraph tracings of ventilation during the FR schedule for Subject RBL. Abscissae: time. Ordinates: continuous flow. Upward pen deflections indicate changes in flow during inspiration; downward pen deflections indicate changes in flow during expiration. Both tracings were derived from a single session. Dark lines on the horizontal axis indicate periods when the FR schedule was in effect (red light illuminated) and responding occurred. Top panel: control breathing during exposure to air after saline administration. Bottom panel: effects of a cumulative dose of 10.0 mg/kg caffeine.

tory rate and minute volume did not depend on predrug values, whereas cocaine, NECA, and CGS 21680 had differential effects associated with different predrug values.

Fixed-Interval Schedule

Responding during the FI 300-s schedule was characteristic of performance maintained under FI schedules of stimulus termination in monkeys (Morse & Kelleher, 1966). Little or no responding occurred early in the interval, and response rate increased as the interval elapsed. Compared to FR performance, the FI schedule engendered lower response rates in all subjects. Mean response rates during control sessions for individual subjects ranged from 0.3 to 1.0 responses per second (Table 1).

Cumulative records of FI performance in Subject RLM illustrate the pattern of responding typically maintained during control sessions, and the effects of caffeine (3.0 to 30.0 mg/kg) administration using a cumulative-dosing procedure (Figure 4). Response rate for Subject RLM tended to be slightly higher during the first component of a session, but saline

administration at the beginning of successive timeouts had no systematic effect on response pattern or rate. Similarly, low doses of caffeine (3.0 to 10.0 mg/kg) had little or no effect on responding. However, the highest dose of caffeine (30.0 mg/kg) completely suppressed responding.

Polygraph tracings of ventilation in Subject RJF illustrate characteristic changes in respiration associated with FI performance (Figure 5). During control sessions, ventilation typically was uniform and stable during the 10-min extended timeout (Figure 5, top). However, there were episodic increases in ventilation during periods of schedule-controlled responding due to increases in respiratory rate and tidal volume (Table 1). In addition, the increases in ventilation during FI performance appeared to be greater in the latter part of the FI when response rate was greater; these increases were separated by the 2-s reinforcement light and the brief 1-min timeout during which ventilation decreased. In the example shown, a cumulative dose of 10.0 mg/kg caffeine increased ventilation during the extended

Table 2

Drug effects on mean ($\pm$ SD) tidal volume and minute volume in a group of 3 monkeys during exposure to air. Control values are the same as in Table 1. Data are shown for the highest dose of each drug administered and are based on two or more observations in each subject.

Condition	Tidal volume (mL/breath)	Minute volume (L/min)
Control (saline)		
FR component	113.3 $\pm$ 14.6	3.9 $\pm$ 0.5
FR timeout	102.2 $\pm$ 10.1	2.7 $\pm$ 0.3
FI component	152.7 $\pm$ 10.5	4.7 $\pm$ 0.8
FI timeout	138.5 $\pm$ 8.4	3.7 $\pm$ 0.4
Caffeine (30.0 mg/kg)		
FR component	126.6 $\pm$ 9.3	7.4 $\pm$ 0.7
FR timeout	118.4 $\pm$ 7.7	7.2 $\pm$ 1.4
FI component	165.3 $\pm$ 17.4	7.8 $\pm$ 1.1
FI timeout	158.2 $\pm$ 19.1	8.1 $\pm$ 1.2
Cocaine (1.0 mg/kg)		
FR component	93.9 $\pm$ 8.7	3.8 $\pm$ 0.5
FR timeout	96.7 $\pm$ 7.3	3.5 $\pm$ 0.5
FI component	135.2 $\pm$ 4.9	5.8 $\pm$ 0.8
FI timeout	129.0 $\pm$ 8.3	4.4 $\pm$ 0.6
NECA (0.03 mg/kg)		
FR component	91.1 $\pm$ 7.4	3.1 $\pm$ 0.5
FR timeout	85.8 $\pm$ 9.9	3.0 $\pm$ 0.7
FI component	109.4 $\pm$ 11.4	3.9 $\pm$ 0.3
FI timeout	104.9 $\pm$ 8.7	4.1 $\pm$ 1.0
CGS 21680 (0.1 mg/kg)		
FR component	93.4 $\pm$ 5.7	3.4 $\pm$ 0.3
FR timeout	87.2 $\pm$ 7.4	3.3 $\pm$ 0.7
FI component	114.0 $\pm$ 6.6	4.0 $\pm$ 0.4
FI timeout	117.1 $\pm$ 8.2	4.1 $\pm$ 0.9

timeout and during the FI component, but the episodic increases in ventilation associated with schedule-controlled responding were still evident (Figure 5, bottom).

Compared to FR performance, control respiratory rate was lower during FI performance even though respiratory rate was similar during the extended timeouts that preceded FI and FR responding (Table 1). The latter results likely reflect the lower response rate engendered by the FI schedule. However, the greater tidal volumes obtained in experiments with the FI schedule were closely associated with physical growth and maturation rather than with the change in reinforcement schedule. Over the 2-year course of the study, mean body weight for the group of 3 subjects increased by 39%; mean tidal volume increased by 36% during the extended timeout when respiration should not have been affected by the performance component of the schedule.

In contrast, respiratory rate during the extended timeout remained stable throughout the 2-year study. Similar increases in tidal volume associated with growth and weight gain have been observed in untrained rhesus monkeys (unpublished observation), further indicating that the change in reinforcement schedule was not responsible for the greater tidal volumes obtained in the FI experiments.

The drugs studied under the FR schedule were also studied under the FI 300-s schedule (Figure 6). Lower doses of caffeine (3.0 and 10.0 mg/kg) produced little or no increase in mean FI response rate for the group, and higher doses (17.0 and 30.0 mg/kg) decreased response rate below control values (Figure 6A). Low and intermediate doses of cocaine (0.1 and 0.3 mg/kg) produced marked increases in FI response rate, and the highest dose (1.0 mg/kg) decreased response rate below control values (Figure 6B). In contrast, NECA and CGS 21680 produced only dose-dependent decreases in FI response rate over the range of doses studied (Figure 6C and D). As FI response rate decreased due to drug administration, each measure of ventilation differed little during FI components and extended timeouts (Figure 6, Table 2). In contrast, the difference in respiratory rate during FI components and extended timeouts was greater after doses of cocaine (0.1 and 0.3 mg/kg) that markedly increased response rate. The highest dose of cocaine (1.0 mg/kg) did not suppress responding to the extent obtained with the other drugs studied, and ventilation remained greater during the FI component compared to the extended timeout (Figure 6B, Table 2). Drug-induced increases in respiratory rate were similar during the extended timeouts of the FI and FR schedules. However, in contrast to the results obtained under the FR schedule, each of the drugs also produced dose-dependent increases in respiratory rate during the performance component of the FI schedule. Given the inverse relationship between predrug respiratory rate and the respiratory effects of cocaine, NECA, and CGS 21680 under the FR schedule, the results under the FI schedule likely reflect the lower baseline respiratory rate compared to the FR schedule.

Fixed-Interval Schedule plus CO₂ Exposure

Exposure to 4% CO₂ mixed in air during the extended timeouts increased ventilation to

FIXED-RATIO SCHEDULE

Fig. 3. Drug effects on mean response rate ($\square$) maintained by an FR 40 schedule of stimulus termination, and mean respiratory rate during extended timeouts ($\circ$) and FR components ($\bullet$), in a group of 3 monkeys. Abscissae: cumulative dose, log scale. Right ordinates: mean response rate (responses per second). Left ordinates: mean respiratory rate (breaths per minute). SAL: mean control values ($\pm$ SD) obtained following saline administration based on at least 10 determinations.

levels greater than those obtained during FI performance and resulted from increases in respiratory rate and tidal volume (Table 3). Polygraph tracings of ventilation in Subject RJF illustrate CO_2 -induced changes in respiration during the extended timeout (Figure 7). The increases in ventilation were rapid in onset and were stable during the 10-min period of exposure. For the group of 3 subjects, mean respiratory rate increased from 23.1 during the extended timeout to 30.5 during exposure to CO_2 . In separate experiments, exposure to 4% CO_2 during FI components also increased ventilation (Table 3). Moreover, the combined effects of CO_2 exposure and FI performance appeared to be additive, because the absolute increase in respiratory rate induced by CO_2 was comparable during extended timeouts (7.4) and FI components (7.9) even though the baseline respiratory rate was greater during the latter condition.

The respiratory-stimulant effects of caffeine (10.0 and 30.0 mg/kg) were compared under each of the experimental conditions utilizing the FI schedule (Figure 8). The effects of FI performance on caffeine-induced increases in respiratory rate appeared to be additive, as shown by the parallel shift in the caffeine dose-effect curve (Figure 8, top). Similarly, exposure to CO_2 enhanced the caffeine-induced increases in respiratory rate during extended timeouts (Figure 8, middle) and during FI components (Figure 8, bottom) at the highest dose of caffeine (30.0 mg/kg).

DISCUSSION

Ventilation measured with the head plethysmograph provided a useful method for studying the effects of schedule-controlled behavior on respiration in nonhuman primates. Episodic increases in ventilation were closely

FIXED-INTERVAL

Fig. 4. Cumulative records of lever pressing in Subject RLM that display the effects of saline administration (top) and cumulative doses of caffeine (bottom) on responding maintained by an FI 300-s schedule of stimulus termination. The response pen deflected upon successful avoidance of the electric stimulus. Other details as in Figure 1.

Table 3

Control ventilation values during exposure to CO₂. Mean ($\pm$ SD) respiratory rate, tidal volume, and minute volume are derived from control (saline) sessions and are based on two or more observations in each subject.

Condition	Subject	Respiratory rate (breaths/min)	Tidal volume (mL/breath)	Minute volume (L/min)
FI component (air)	RBL	20.5 $\pm$ 0.7	165.2 $\pm$ 2.3	3.4 $\pm$ 0.2
	RJF	39.5 $\pm$ 6.4	144.6 $\pm$ 2.7	5.7 $\pm$ 1.0
	RLM	24.0 $\pm$ 0.0	168.5 $\pm$ 18.9	4.0 $\pm$ 0.4
	Group	28.0 $\pm$ 2.4	159.4 $\pm$ 13.4	4.5 $\pm$ 0.6
FI component (CO ₂)	RBL	28.7 $\pm$ 4.0	264.6 $\pm$ 31.2	7.6 $\pm$ 0.9
	RJF	44.9 $\pm$ 2.7	236.3 $\pm$ 17.8	10.6 $\pm$ 0.4
	RLM	34.2 $\pm$ 2.6	315.4 $\pm$ 10.1	10.8 $\pm$ 1.1
	Group	35.9 $\pm$ 3.2	272.1 $\pm$ 12.2	9.8 $\pm$ 0.8
Timeout (air)	RBL	18.5 $\pm$ 2.1	158.2 $\pm$ 4.9	2.9 $\pm$ 0.3
	RJF	32.0 $\pm$ 1.4	127.8 $\pm$ 18.3	4.1 $\pm$ 0.4
	RLM	19.0 $\pm$ 0.0	140.0 $\pm$ 36.9	2.7 $\pm$ 0.8
	Group	23.1 $\pm$ 1.2	142.0 $\pm$ 17.8	3.3 $\pm$ 0.7
Timeout (CO ₂)	RBL	26.0 $\pm$ 3.3	271.2 $\pm$ 4.9	7.1 $\pm$ 0.8
	RJF	39.7 $\pm$ 2.2	230.4 $\pm$ 36.5	9.1 $\pm$ 1.0
	RLM	25.7 $\pm$ 2.8	320.2 $\pm$ 39.2	8.2 $\pm$ 0.2
	Group	30.5 $\pm$ 2.6	273.9 $\pm$ 15.0	8.4 $\pm$ 0.7

Fig. 5. Polygraph tracings of ventilation during the FI schedule for Subject RJJ. Regions on the horizontal axis identified as Fixed Interval indicate periods when the FI schedule was in effect and responding occurred. Each FI was separated by a 60-s timeout. Top panel: control breathing during exposure to air after saline administration. Bottom panel: effects of a cumulative dose of 10.0 mg/kg caffeine. Other details as in Figure 2.

associated with periods of schedule-controlled responding; ventilation was greater during the performance components of daily sessions compared to the extended timeouts that preceded performance components. Drug-induced suppression of behavior eliminated the episodic increases in ventilation during the performance components of both schedules, further demonstrating a close correspondence between behavior and respiration. Exposure to elevated levels of CO_2 in inspired air reliably increased ventilation in all subjects, and the effects of CO_2 exposure and schedule-controlled responding on respiratory rate appeared to be additive. The results demonstrate that increased behavioral activity associated with schedule-controlled performance can produce concomitant increases in ventilation that may involve CO_2 -sensitive mechanisms.

Previous studies have reported episodic changes in cardiovascular activity during periods of schedule-controlled performance in nonhuman primates (Forsyth, 1969; Herd et al., 1969; Kelleher et al., 1972), and the present study extends these findings to measures of respiration in rhesus monkeys. Herd et al. (1969) reported increases in blood pressure in

squirrel monkeys in association with characteristic patterns of FR responding under a stimulus-termination schedule. Moreover, there was a general correspondence between rate of responding and mean arterial blood pressure. However, in the later phases of training in some subjects studied under an FI schedule, blood pressure was elevated not only during periods of responding but also during timeouts scheduled between FI components. Additional studies continuously measured blood pressure 24 hr per day and found that hypertension persisted when the subjects were returned to their home cages (Herd, Morse, Kelleher, & Grose, 1971). The latter results contrast markedly with the transient changes in ventilation obtained in the present study. Polygraph recordings illustrate recurring episodes of increased ventilation in phase with FR responding, separated by the 5-s reinforcement light and the brief 10-s timeout during which ventilation decreased. Under the FI schedule, both ventilation and response rate typically increased as the 300-s interval elapsed. Under both schedules, increases in ventilation during the performance components were not sustained during the extended timeouts. The

FIXED-INTERVAL SCHEDULE

Fig. 6. Drug effects on mean response rate ($\square$) maintained by an FI 300-s schedule of stimulus termination and mean respiratory rate during extended timeouts ($\circ$) and FI components ($\bullet$). Other details as in Figure 3.

rapid and reversible changes in respiration differ considerably from the long-term changes in cardiovascular activity reported previously, and may reflect separate regulatory mechanisms influenced by the experimental procedures.

Several drugs with behavioral and respiratory effects were studied in subjects with schedule-related elevations in ventilation to investigate further the interactions between behavior and respiration. Adenosine and the cyclic nucleotide system reportedly play a major role in the control of respiration (Griffiths & Holgate, 1990). Adenosine agonists stimulate respiration in primates ostensibly through activation of peripheral O_2 -sensitive mechanisms (Howell, 1993b). Moreover, the behavioral-stimulant effects of xanthines have been linked to blockade of central adenosine receptors (Daly, Bruns, & Snyder, 1981; Snyder et al., 1981), and metabolically stable analogues of adenosine are potent behavioral depressants

(Goldberg et al., 1985; Spealman, 1988). Caffeine and related xanthines also stimulate respiration in primates, but their effects likely involve central CO_2 -sensitive mechanisms and are linked to inhibition of cyclic nucleotide PDE (Howell, 1993a; Howell et al., 1990). Accordingly, the present study characterized the behavioral and respiratory effects of caffeine and two adenosine agonists, NECA and CGS 21680. Cocaine was also studied because of its pronounced behavioral-stimulant effects that are not believed to involve the cyclic nucleotide system directly (Ritz et al., 1987; Woolverton & Kleven, 1988). Each of the four drugs produced dose-dependent decreases in FR response rate, and the highest dose of each drug markedly suppressed responding in all subjects. As response rate decreased, the difference in ventilation during FR components and extended timeouts diminished. Each of the drugs also produced dose-dependent increases in ventilation during the extended timeouts.

Fig. 7. Polygraph tracings of ventilation during the FI schedule for Subject RJF. Regions on the horizontal axis identified as Fixed Interval indicate periods when the FI schedule was in effect and responding occurred. Top panel: exposure to air only. Bottom panel: exposure to CO_2 during the extended timeout. Arrows indicate the period of CO_2 exposure.

Hence, the diminished difference in respiratory rate during FR components and extended timeouts likely involved the joint actions of decreased responding and direct respiratory effects of increasing doses of drug.

It is particularly noteworthy that similar results were obtained with several drugs that have different biochemical actions and pharmacological profiles. Caffeine produced marked increases in respiratory rate and minute volume during extended timeouts and during FR components. In contrast, cocaine, NECA, and CGS 21680 had either no effect or slightly decreased respiratory rate and minute volume during FR components. The difference between caffeine and NECA under the two conditions is in agreement with reported effects of caffeine and NECA on ventilation in untrained rhesus monkeys exposed to air or elevated levels of CO_2 mixed in air (Howell et al., 1990). Caffeine produced marked increases in respiratory rate during both conditions, whereas NECA had less pronounced effects on respiratory rate when ventilation was stimulated by CO_2 . Taken together, the results demonstrate comparable drug effects on respiration stimulated by CO_2 or schedule-controlled behavior.

Changing the schedule from FR 40 to FI

300 s engendered lower response rates in all subjects and provided a sensitive baseline for measuring drug-induced increases in response rate. In addition, the difference in respiratory rate during performance components and extended timeouts was less than that obtained with the FR schedule, ostensibly due to the lower response rate engendered by the FI schedule. Cocaine produced marked increases in FI response rate, and the difference in respiratory rate during FI components and extended timeouts increased when response rate increased. The latter results further demonstrate a close correspondence between ventilation and rates of schedule-controlled behavior, and extend the finding obtained with FR performance to conditions in which responding increased following drug administration. In contrast to the effects of cocaine, both NECA and CGS 21680 only decreased FI responding. Caffeine produced slight increases in response rate at low and intermediate doses, but markedly decreased response rate at the highest dose studied. Consistent with the results obtained under the FR schedule, the difference in ventilation during FI components and extended timeouts generally diminished as FI response rate decreased.

Schedule-related increases in ventilation

Fig. 8. Effects of cumulative doses of caffeine on mean respiratory rate in a group of 3 monkeys. Abscissae: cumulative dose. Ordinates: mean respiratory rate (breaths per minute). Top panel: mean respiratory rate during extended timeouts (○) and FI components (●) when subjects breathed air only. Middle panel: mean respiratory rate during extended timeouts when subjects breathed air only (○) or 4% CO₂ mixed in air (●). Bottom panel: mean respiratory rate during FI components when subjects breathed air only (○) or 4% CO₂ mixed in air (●). SAL: mean control values ($\pm SD$) obtained following saline administration based on at least three determinations.

were compared to those produced by elevated levels of CO₂ in inspired air to investigate physiological mechanisms that may mediate the observed changes in ventilation associated with schedule-controlled behavior. The chemical regulation of ventilation involves central chemoreceptors that respond to changes in arterial CO₂ tensions (Mueller et al., 1982). Because CO₂ production is a consequence of oxidative metabolism, sustained behavior could directly stimulate ventilation through increased metabolic demand associated with skeletal muscle activity. In the present study, exposure to elevated levels of CO₂ in inspired air reliably increased ventilation in all subjects, and the effects of CO₂ exposure and schedule-controlled behavior on ventilation appeared to be additive. Moreover, the CO₂-induced increases in ventilation were comparable during extended timeouts and FI components, even though the baseline ventilation was greater during the latter condition. The time course of respiratory stimulation due to CO₂ exposure or schedule-controlled behavior was also very similar. Increases in ventilation associated with schedule-controlled responding were sustained for no more than 1 or 2 min into the subsequent extended timeout. Similarly, changing the inspired gas from 4% CO₂ mixed in air to air alone resulted in a rapid decrease in ventilation to control values within 1 or 2 min. The latter results correspond closely with the reported time course of effects of 5% CO₂ mixed in air on ventilation in untrained rhesus monkeys (Howell et al., 1988).

Finally, the respiratory-stimulant effects of caffeine were studied under each of the experimental conditions with the FI schedule, and the effects of FI performance on caffeine-induced increases in respiratory rate appeared to be additive. Similarly, exposure to CO₂ enhanced caffeine-induced increases in respiratory rate at the highest dose studied. Previous reports have shown that caffeine's respiratory-stimulant effects likely are mediated through central CO₂-sensitive mechanisms (Lundberg, Breese, & Mueller, 1981; Wessberg, Hedner, Hedner, Persson, & Jonason, 1985), and the combined effects of caffeine and CO₂ on respiration in primates appear to be additive (Howell, 1993a; Howell et al., 1990). The enhanced effects of caffeine during both CO₂-induced and behaviorally induced hyperven-

tilation in the present study further implicate CO₂ production as a possible mechanism mediating the concomitant increases in ventilation that are associated with schedule-controlled behavior.

In summary, the head plethysmograph provided a useful method for studying the effects of schedule-controlled behavior on respiration in nonhuman primates. Episodic increases in ventilation were closely associated with periods of schedule-controlled responding under FR and FI schedules of stimulus termination. Moreover, drug-induced suppression of behavior eliminated the episodic increases in ventilation during the performance components of both schedules. Exposure to elevated CO₂ in inspired air increased ventilation in all subjects, and the effects of CO₂ exposure and schedule-controlled responding appeared to be additive. The results suggest that behavioral activities may stimulate ventilation directly through increased metabolic demand and increased CO₂ production.

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Received January 26, 1993

Final acceptance February 15, 1994