Pharmacological dissociation of heart rate and somatomotor components of the orienting response

JANE A. SAIERS, RICK RICHARDSON, and BYRON A. CAMPBELL
Princeton University, Princeton, New Jersey

In response to a discrete auditory stimulus, rats exhibit a quick, lateral head jerk and a 40-50-bpm deceleration in heart rate (HR). Both the head jerk and the bradycardia are components of the orienting response (OR), which is presumed to reflect stimulus-directed attention. The present research examined the effects of cholinergic and dopaminergic blockade on the OR to an 80-dB tone. In Experiment 1, scopolamine hydrobromide was found to inhibit the HR OR in a dose-dependent manner ranging from little effect at 0.05 mg/kg to complete inhibition of the cardiac OR at 0.5 mg/kg. The head-jerk response, unlike the cardiac response, was undiminished by scopolamine. In the second experiment, haloperidol, administered at dosages ranging from 0 to 10 mg/kg, attenuated the behavioral response (head jerk) in a dose-dependent fashion but had no effect on the cardiac component of the OR. These results demonstrate that the autonomic and behavioral components of the OR are independent representations of a common central process unaffected by cardiosomatic coupling. The results also demonstrate that neither the cardiac nor the somatomotor component of the OR is dependent upon the integrity of central cholinergic or dopaminergic neurotransmission.

During the last decade, the heart rate orienting response (HR OR) has reemerged in psychophysiological and bi-behavioral research as a useful index of stimulus-directed attention (Turpin, 1983). In the past, however, most stimulus-induced, vagally mediated changes in HR were believed to be inextricably coupled with changes in somatic activity; therefore, HR was "a useful biological parameter only to the extent it [was] important to know whether somatic activities had been modified" (Obrist et al., 1974, p. 161).

Although subsequent research prompted modification of this view, experimenters employing HR as a dependent measure continue to be concerned about the possibility of cardiosomatic coupling as an alternative explanation for their results. Some researchers, for example, tested rats for the HR OR while the animals were engaged in slow-wave sleep in order to minimize HR alterations associated with movement during waking (Rockstroh et al., 1987). In addition, Dailey, Wigal, and Amsel (1986) compared baseline HRs in their rats with activity levels in order to rule out a "cardiosomatic linkage" explanation for their results.

In most OR experiments employing behavioral measures to approach the cardiosomatic coupling problem, attempts are made to correlate the degree of somatomo-

tor activity with HR levels during stimulus presentation (see Siegel, Sananes, Gaddy, & Campbell, 1987, for example). Although magnitude of the HR OR has been shown in these experiments not to be a function of amount of stimulus-elicited somatic activity, pharmacological dissociation of HR and behavioral components of the OR has not been demonstrated. Unlike behavioral approaches to the cardiosomatic coupling problem, pharmacological approaches allow complete dissociation of cardiac and behavioral components of the OR. Therefore, the independence of stimulus-evoked changes in HR and somatomotor activity can be unequivocally demonstrated. Does the organism behaviorally orient to a stimulus when HR deceleration has been pharmacologically prevented? Similarly, does stimulus-induced bradycardia occur when the behavioral OR is prevented by drug-induced immobility?

In the following experiments, pharmacological dissociation of HR and the behavioral components of the OR to a pulsating tone was attempted in rats. The pulsating tone used in these experiments has consistently been shown to produce a robust (40-60 bpm) bradycardic HR OR accompanied by a quick, lateral head jerk—a discrete response followed by a variable period of time in which the animal remains relatively motionless (e.g., Richardson, Siegel, & Campbell, 1988; Siegel et al., 1987). In Experiment 1, the effect of scopolamine hydrobromide, which blocks both central and peripheral cholinergic receptors, on the OR was assessed. Scopolamine prevents vagally mediated phasic changes in HR, such as the HR OR (Haroutunian & Campbell, 1982), but it has no effect on either voluntary or involuntary movement. Therefore, it was hypothesized that if the HR and be-

This research was partly supported by U.S. Public Health Service Grant MH-01562 to Byron A. Campbell. Jane A. Sakers was supported by a National Science Foundation Graduate Fellowship and Rick Richardson was supported by National Research Service Award AG-05417. Reprint requests should be sent to Byron A. Campbell, Department of Psychology, Princeton University, Princeton, NJ 08544-1010.

havioral ORs are independent measures of stimulus-directed attention, scopolamine hydrobromide would attenuate the HR OR but would leave the behavioral OR intact. In the second experiment, the effect of haloperidol, a dopaminergic receptor blocker, on the OR was explored. Destruction of dopaminergic pathways in rats results in a "sensory inattention" syndrome in which rats fail to motorically attend to or investigate somatosensory, visual, or olfactory stimuli (Marshall, 1979; Marshall & Gotthelf, 1979). However, since dopamine-depleted animals can learn (e.g., Price & Fibiger, 1975), they must retain at least some attentional capacity. Therefore, dopamine receptor blockade should inhibit the behavioral OR (the head jerk) without affecting the HR OR.

EXPERIMENT 1

Method

Subjects. Forty-eight, 16- to 17-day-old (day of birth = Day 0) Sprague-Dawley rats born and reared in the animal colony of the Psychology Department at Princeton University were used as subjects. Litters were culled to 8 pups on Day 2, and pups were housed with the dam in $45 \times 24 \times 21$ cm plastic cages. The rats were maintained on a 16:8 day:night cycle, with lights on at 0730 h, and had ad libitum access to food and water. The animals were randomly assigned to one of four conditions, with 12 animals per condition, and no more than 2 pups from a litter served in any one condition. The animals were tested between 0800 and 1500 h.

Apparatus. A clear Plexiglas box ($21.5 \times 20.3 \times 24.7$ cm) served as the test apparatus. The box was contained within a single-wall, sound-attenuating Industrial Acoustics Chamber (IAC) with a double-paned window through which the animal was observed. The chamber was illuminated by a 6-W light bulb.

The auditory stimulus was an 80-dB (as measured on Scale C of a Simpson sound level meter), 1600-Hz tone pulsating at a rate of 2 pulses/sec for 10 sec. The tone was generated by a Coulbourn Instruments precision signal generator, amplified by a Radio Shack audio amplifier, and delivered through a 16.5-cm speaker inside the IAC. Stimulus presentation was controlled by a Commodore CBM microcomputer.

HR was recorded using two transcutaneous stainless steel electrodes (25 ga) in the shape of safety pins with attached leads of 32-ga teflon-coated wire (No. 2840/7, Alpha). Cardiac potentials were amplified by a Grass preamplifier (Model P511K), and the signal was displayed on a Hitachi oscilloscope (Model V-212). The R-spike activated a Schmitt trigger (Coulbourn Instruments), the output of which was recorded by a Commodore CBM microcomputer. The microcomputer measured the interbeat intervals (IBIs) to the nearest millisecond during a 5-sec prestimulus period and the 10-sec stimulus presentation. For each trial, the mean HR (in beats per minute) during the prestimulus period was subtracted from the mean HR during the stimulus presentation to determine the magnitude of the HR OR.

During the 5-sec prestimulus period and the 10-sec stimulus presentation, the animals were observed for head jerks. The head-jerk response is a sudden lateral movement of the head that occurs in the absence of other gross body movement (Saiers, Richardson, & Campbell, in press; Siegel et al., 1987). To determine the percentage of animals performing head jerks in each condition, the number of animals displaying the head jerk during the stimulus period was divided by the number of subjects (12) per condition and multiplied by 100.

Scopolamine hydrobromide, obtained from Sigma Chemicals, was diluted in isotonic saline.

Procedure. The rats were randomly assigned to one of four conditions in which they received (i.p.) 0, 0.05, 0.10, or 0.50 mg/kg (free base) of scopolamine hydrobromide. The rats were injected with the appropriate dose of scopolamine and were immediately returned to the litter and dam for 15 min. After 15 min, the rat was removed from the litter and implanted with HR recording electrodes, a relatively painless and quick (10-sec) procedure. One electrode was implanted dorsally, at the nape of the neck, and the other ventrally, anterior to the urogenital region. Following implantation, the rat was placed into the Plexiglas test apparatus, to which it adapted for 15 min.

After the adaptation period, the rat was presented with four, 10-sec pulsating tones separated by 60-sec interstimulus intervals. During stimulus presentation for each of the four trials, the rat was observed for head jerks.

Results

Because both HR and the behavioral OR habituate rapidly (see Figures 6 and 7), data analysis was performed only on the responses to the first tone presentation. At a dosage of 0.50 mg/kg of scopolamine hydrobromide, the HR OR was completely abolished (see Figure 1). Increasingly less attenuation of the HR OR occurred at the 0.10 and 0.05 mg/kg doses, and saline-treated animals exhibited a full HR OR. A one-way ANOVA performed on the HR OR data was significant [$F(3,44) = 11.37$, $p < .001$].

The behavioral OR, unlike the HR OR, was not affected by scopolamine (See Figure 2). Consistently, whether they received saline or any of the three doses of scopolamine, 75%–80% of the animals in each condition performed head jerks. The chi-square test performed on the data was nonsignificant [$\chi^2(3) = .35$, $p > .05$].

Scopolamine hydrobromide reduced baseline HRs (see Figure 3) in all three drug conditions, relative to the saline condition. This finding was unexpected, since in prior research, methyl scopolamine had no effect on basal HR in 19-day-old rats (Haroutunian & Campbell, 1982). The fact that baseline HR did not covary systematically with dosage suggests that the decrease in HR in this experi-

Figure 1. Magnitude of the heart rate orienting response (change from baseline heart rate in beats per minute) to an 80-dB tone as a function of dose (mg/kg) of scopolamine hydrobromide.

Figure 2. Occurrence of the behavioral orienting response (percentage of animals showing head jerk) to an 80-dB tone as a function of dose (mg/kg) of scopolamine hydrobromide.

Figure 3. Baseline heart rate as a function of dose (mg/kg) of scopolamine hydrobromide.

ment may have been coincidentally, rather than causally, linked to cholinergic blockade. A one-way ANOVA performed on the baseline data was significant [$F(3,44) = 3.54$, $p < .05$].

Discussion

Scopolamine hydrobromide attenuated the HR OR in a dose-dependent manner. A dose of 0.50 mg/kg completely abolished the HR OR, and increasingly less HR OR attenuation occurred at doses of 0.10 and 0.05 mg/kg scopolamine. These findings corroborate those of Haroutunian and Campbell (1982), who reported that the HR OR in 19–20-day-old rats was similarly attenuated by comparable doses of methyl scopolamine, the peripherally acting form of the drug.

Although scopolamine blocks the HR OR, the behavioral OR is not inhibited by the drug. Regardless of the dosage of scopolamine, nearly 80% of the animals in all conditions in this experiment exhibited head jerks in response to the pulsating tone. Unlike peripherally acting methyl scopolamine, the scopolamine hydrobromide

used in this experiment also blocks central cholinergic receptors. The persistence of the behavioral OR in spite of central cholinergic blockade indicates that the integrity of the central cholinergic system is not essential for stimulus-directed attention.

EXPERIMENT 2

The dissociation of somatomotor and cardiac activity can be further delineated by the complementary demonstration of an intact HR OR in the absence of a behavioral OR. In Experiment 2, haloperidol was used in an attempt to pharmacologically inhibit the head-jerk response to a pulsating tone without affecting the HR response. In this case, skeletomotor feedback could not account for the deceleratory change in HR in response to stimulus presentation if a change in skeletomotor activity is prevented by haloperidol.

Method

Subjects. The subjects were 40 16- to 17-day-old Sprague-Dawley rats born in the Psychology Department vivarium at Princeton University and raised under the same conditions as the animals in Experiment 1. The pups were randomly assigned to one of four conditions, and no more than 2 pups from a litter served in any condition.

Apparatus. The apparatus was the same one used in Experiment 1, and the HR data were collected and analyzed as in the previous experiment.

Haloperidol was obtained in the commercially available form (Hal-dol) from McNeil Pharmaceuticals and was diluted in isotonic saline.

Procedure. The animals were randomly assigned to four conditions in which they received 0, 0.5, 0.8, or 1.0 mg/kg haloperidol. Except for the type of drug administered, the procedures were identical to those of Experiment 1. After this experiment was completed, a fifth drug dosage (10.0 mg/kg) was tested using the same procedures to examine the magnitude of the HR OR in the akinetic animal.

Results

Again, Trial 1 results were analyzed; the 10.0-mg/kg data were omitted from statistical analyses because they were obtained at a different time. Haloperidol had no effect on the HR OR at any dose (see Figure 4). All animals

Figure 4. Magnitude of the heart rate orienting response (change from baseline heart rate in beats per minute) to an 80-dB tone as a function of dose (mg/kg) of haloperidol.

given haloperidol displayed an unattenuated HR OR, relative to saline controls, in response to the pulsating tone. A one-way ANOVA performed on the HR OR data was nonsignificant ($F < 1$).

Haloperidol did, however, attenuate the behavioral OR in a dose-dependent manner (see Figure 5): none of the rats given 1.0 or 10.0 mg/kg haloperidol exhibited a head jerk in response to the tone, and an increasingly greater percentage of animals performed head jerks at the 0.8 and 0.5 mg/kg doses. Almost all of the saline controls behaviorally oriented to the tone. The chi-square test performed on the head-jerk data was significant [$\chi^2(3) = 15.56, p < .05$].

Baseline HRs between conditions were not significantly different ($F < 1$).

Discussion

Haloperidol, although it did not affect the HR OR, attenuated the behavioral OR in a dose-dependent manner: 1.0 mg/kg haloperidol abolished the head-jerk response to an auditory stimulus, and increasingly less inhibition occurred in the 0.8- and 0.5-mg/kg conditions. All four doses of haloperidol caused immobility in the animals long before the first stimulus presentation. Contrary to the cardiosomatic coupling hypothesis, then, the bradycardia that occurred upon presentation of the auditory stimulus cannot be attributed to a stimulus-evoked change in skeletomotor activity. In fact, in all drug conditions, 90% of the animals were immobile during the 5 sec immediately preceding the tone, whereas only 50% of the saline-treated animals were immobile before tone presentation. The magnitude of the HR OR, however, was almost identical across conditions regardless of whether a stimulus-evoked change in skeletomotor activity occurred. That haloperidol-treated animals were, indeed, aware of the stimuli was evident only in their HR responses to them.

The present experimental findings demonstrate that, at least in the case of the OR, dissociation of cardiac and somatomotor activity is induced quite easily at the rather

minimal dose of 1.0 mg/kg haloperidol. The magnitude of the deceleratory HR response to the auditory stimulus attests to the independence of the HR and somatomotor components of the OR. Animals in all conditions in this experiment exhibited about a 50-bpm deceleration in HR in response to the tone, without a simultaneous change in skeletomotor activity.

GENERAL DISCUSSION

The data from these experiments establish the independence of the cardiac and behavioral components of the OR to an auditory stimulus. In Experiment 1, the behavioral OR to a pulsating tone maintained its robustness despite a total blockade of the HR OR by scopolamine hydrobromide (0.5 mg/kg). In Experiment 2, the behavioral OR was abolished by haloperidol (1.0 mg/kg), but the HR OR was unattenuated. These results indicate that these two components of the OR independently index some aspect of stimulus-directed attention, and that neither of them is simply the result of autonomic-somatomotor coupling.

Pribram (Pribram & McGuinness, 1975) also obtained dissociation of HR and behavioral ORs by lesioning the orbitofrontal cortex and amygdala in monkeys. These lesions abolished the HR, but not the behavioral, OR; however, they also prevented habituation of the behavioral OR. In the present study, in contrast, a symmetrical dissociation was achieved between the behavioral and the autonomic components of the OR. When either the behavioral or the HR component of the OR was inhibited, the rate of habituation of the intact component was the same as that seen when both elements were elicited simultaneously in the saline-treated animals. For example, haloperidol, which eliminated the head-jerk component of the OR, did not alter the rate of habituation of the HR response to the auditory stimulus. These data are shown in Figure 6. Conversely, scopolamine, which eliminated the HR OR, did not affect habituation of the head-jerk response (Figure 7).

The results of Experiment 2 are also relevant to the lesion work performed on the dopamine-rich extrapyramidal system. Lesions of the substantia nigra, neostriatum, and lateral hypothalamus impair somatomotor orienting to tactile, visual, and olfactory stimuli in rats (Marshall, 1979; Marshall, Berrios, & Sawyer, 1980; Marshall & Gotthelf, 1979). The behavioral syndrome produced by these lesions has been variously described as "sensory inattention," "sensory neglect," and a failure in sensory-motor integration. The fact that, in this study, akinetic haloperidol-treated animals demonstrated a normal HR OR to auditory stimulus presentation indicates that DA-impaired animals remain fully attentive to stimuli in spite of their motoric incapacity (also see Carli, Evenden, & Robbins, 1985, for further evidence that striatal lesions do not impair sensory attention).

If it is assumed that the behavioral and autonomic ORs are manifestations of central stimulus detection and/or processing, the results of the present study fail to impli-

Figure 5. Occurrence of the behavioral orienting response (percentage of animals showing head jerk) to an 80-dB tone as a function of dose (mg/kg) of haloperidol.

Figure 6. Magnitude of the heart rate orienting response (change from baseline heart rate in beats per minute) to an 80-dB tone after haloperidol (left panel) or scopolamine hydrobromide (right panel) injection as a function of trial.

Figure 7. Occurrence of the behavioral orienting response (percentage of animals showing headjerk) to an 80-dB tone after haloperidol (left panel) or scopolamine hydrobromide (right panel) injection as a function of trial.

cate either dopaminergic or cholinergic transmission as critical components in the central attentional processes. In this study, dosages of scopolamine capable of producing state-dependent learning (Carlton, 1963) did not inhibit the behavioral OR to an auditory stimulus. Similarly, doses of haloperidol sufficient to eliminate overt responding failed to inhibit the cardiac component of the OR. The occurrence of the behavioral OR during central cholinergic blockade, and of the cardiac OR in spite of dopaminergic blockade, indicates that stimulus detection did indeed occur. Neither detection of sensory stimuli nor the rudimentary sensory processing implied by the occurrence

of the OR are prevented by blockade of dopaminergic or cholinergic transmission.

Elliott (1974) emphasized the necessity of defining the bounds of cardiosomatic coupling in order to establish the psychological usefulness of particular phasic changes in HR. Especially in the realms of attention and learning, these bounds have been clearly identified. Conditioned changes in HR, for example, appear not to be skeleto-motor artifacts (Fitzgerald, Stainbrook, & Francisco, 1985; Martin & Fitzgerald, 1980). This study, especially when it is considered in light of previous work on the OR (e.g., Dailey et al., 1986; Siegel et al., 1987), indicates

that the HR OR, too, is not simply a product of skeleto-motor behavior. Rather, both the behavioral and the cardiac components of the OR can be considered robust and reliable measures of some aspect of stimulus-directed attention.

REFERENCES

- CARLI, M., EVENDEN, J. L., & ROBBINS, T. W. (1985). Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. *Nature*, **313**, 679-682.
- CARLTON, P. L. (1963). Cholinergic mechanisms in the control of behavior by the brain. *Psychological Review*, **70**, 19-38.
- DAILEY, W., WIGAL, S. B., & AMSEL, A. (1986). Effects of photic stimulation on heart rate of infant rats. *International Journal of Psychophysiology*, **3**, 183-204.
- ELLIOTT, R. (1974). The motivational significance of heart rate. In P. A. Obrist, A. H. Black, J. Brener, & L. V. DiCara (Eds.), *Cardiovascular psychophysiology* (pp. 505-537). Chicago: Aldine.
- FITZGERALD, R. D., STAINBROOK, G., & FRANCISCO, D. (1985). Classically conditioned bradycardia and skeletal-motor activity in restrained rats. *Physiological Psychology*, **13**, 211-216.
- HAROUTUNIAN, V., & CAMPBELL, B. A. (1982). Neural control of the heart-rate-orienting response in preweanling rats. *Behavioral & Neural Biology*, **36**, 24-39.
- MARSHALL, J. F. (1979). Somatosensory inattention after dopamine-depleting intracerebral 6-OHDA injections: Spontaneous recovery and pharmacological control. *Brain Research*, **177**, 311-324.
- MARSHALL, J. F., BERRIOS, N., & SAWYER, S. (1980). Neostriatal dopamine and sensory inattention. *Journal of Comparative & Physiological Psychology*, **94**, 833-846.
- MARSHALL, J. F., & GOTTHELF, T. (1979). Sensory inattention in rats with 6-hydroxydopamine-induced degeneration of ascending dopaminergic neurons: Apomorphine-induced reversal of deficits. *Experimental Neurology*, **65**, 398-411.
- MARTIN, G. K., & FITZGERALD, R. D. (1980). Heart rate and somato-motor activity in rats during signalled escape and yoked classical conditioning. *Physiology & Behavior*, **25**, 519-526.
- OBRIEST, P. A., HOWARD, J. L., LAWLER, J. E., GALOSY, R. A., MEYERS, K. A., & GAEBELEIN, C. J. (1974). The cardiac-somatic interaction. In P. A. Obrist, A. H. Black, J. Brener, & L. V. DiCara (Eds.), *Cardiovascular psychophysiology* (pp. 136-162). Chicago: Aldine.
- PRIBRAM, K. H., & MCGUINNESS, D. (1975). Arousal, activation, and effort in the control of attention. *Psychological Review*, **82**, 116-149.
- PRICE, M. T. C., & FIBIGER, H. C. (1975). Discriminated escape learning and response to electric shock after 6-hydroxydopamine lesions of the nigro-neostriatal dopaminergic projection. *Pharmacology, Biochemistry & Behavior*, **3**, 285-290.
- RICHARDSON, R., SIEGEL, M. A., & CAMPBELL, B. A. (1988). Unfamiliar environments impair information processing as measured by behavioral and cardiac orienting responses to auditory stimuli in preweanling and adult rats. *Developmental Psychobiology*, **21**, 491-503.
- ROCKSTROH, B., JOHNNEN, M., ELBERT, T., LUTZENBERGER, W., BIRBAUMER, N., RANDOLPH, K., OSTWALD, J., & SCHNITZLER, H. (1987). The pattern and habituation of the orienting response in man and rats. *International Journal of Neuroscience*, **37**, 169-182.
- SAIERS, J. A., RICHARDSON, R., & CAMPBELL, B. A. (in press). Disruption and recovery of the orienting response following shock or context change in preweanling rats. *Psychophysiology*.
- SIEGEL, M. A., SANANES, C. B., GADDY, J. R., & CAMPBELL, B. A. (1987). Dissociation of heart rate and somatomotor orienting responses in preweanling rats. *Psychobiology*, **15**, 122-127.
- TURPIN, G. (1983). Unconditioned reflexes and the autonomic nervous system. In D. Siddle (Ed.), *Orienting and habituation: Perspectives in human research* (pp. 1-70). New York: Wiley.

(Manuscript received July 25, 1988;
revision accepted for publication May 30, 1989.)