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Conditioned Neuroendocrine and Cardiovascular Stress Responsiveness Accompanying Behavioral Passivity and Activity in Aged and in Young Rats

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KORTE, S. M., B. BUWALDA, G. A. H. BOUWS, J. M. KOOLHAAS, F. W. MAES AND B. BOHUS. *Conditioned neuroendocrine and cardiovascular stress responsiveness accompanying behavioral passivity and activity in aged and in young rats.* PHYSIOL BEHAV **51**(4) 815–822, 1992.—Mean arterial pressure (MAP), heart rate (HR), plasma epinephrine (E), plasma norepinephrine (NE), and plasma corticosterone (CORT) were measured in 3-month- and 24-month-old male Wistar rats exposed to a conditioned emotional stress response (CER) paradigm and a conditioned defensive burying (CDB) paradigm. In the CER situation blood samples were taken during reexposure to the training environment one day after a single inescapable footshock (0.6 mA, AC for 3 s) had been administered. In the CER paradigm the young rats displayed passive behavior (immobility) accompanied by an increase in plasma levels of CORT and E, whereas both the control and conditioned animals showed increased NE responses. Previously shocked aged rats exhibited an attenuated plasma NE response, whereas levels of E remained elevated to a greater extent. Aged animals showed elevated basal levels of CORT one day after footshock administration. Stress-induced immobility was preserved in the aged rats. These animals had an increase in basal MAP values and a decrease in basal HR values compared to young ones.

In the CDB paradigm, rats were exposed to a nonelectrified probe 1 day after the repeated shock (2 mA/contact) procedure. Young rats displayed defensive burying accompanied by increments in MAP, HR, CORT, and NE. The aged animals showed similar hormonal, autonomic, and behavioral stress responses.

Thus, the age-related alterations in neuroendocrine and autonomic response patterns are apparent in stressed animals during behavioral passivity in absence of control (CER) rather than during active control (defensive burying).

Stress Aging Blood pressure Heart rate Catecholamines Corticosterone

STRESS, age, and behavioral characteristics are considered to be risk factors for disturbances of the cardiovascular system in animal and man (17,18,31). Previous studies from our laboratory revealed significant interactions between individual responsiveness to a changing environment and susceptibility for high blood pressure in chronically stressed rats (17). During aging the inhibitory influences on cardiac rhythm in response to certain conditioned stressors diminish, either directly due to impairment of the descending vagus tone or indirectly due to a decrease in the central drive of this system (31). Although the biology of aging is a major field of interest, surprisingly few studies have examined autonomic and endocrine responses to stress in aged rodents (7,30). Based on measurements of plasma norepinephrine and epinephrine, there is some evidence to suggest that aged rats are less capable of regulating the sympathoadrenomedullary system during and after exposure to stressors (7,30). In these studies the direct physical consequences of aversive stimulation rather than the consequences of conditioned fear was studied. In order to separate direct effects of the aversive stimulus from the psychological consequences of the punishment, we studied changes in cardiovascular and hormonal parameters in conditioned stress paradigms. The stress responses are determined by interactions between the environment (controllability/predictability), the properties of the stressor (quality, intensity, and duration), and individual differences in coping strategy (3,4,20,43). To test the effects of aging in a situation that is well defined with respect to these interactions we studied stress responses in young and in aged rats in two different conditioned stress paradigms in which the animals display either passive or active behavior.

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METHOD

Animals

Young male adult rats 3 months of age, weighing 301 ± 2 g and rats aged 24 months and weighing 534 ± 30 g were used. The animals were of a Wistar strain [Cpb, TNO, Zeist, The Netherlands] and were bred in our laboratory. Six animals were housed per cage. Group housing was consistent until the beginning of the experimental procedures. In the case of the aged group, housing was consistent over the 24-month period. After surgery they were placed individually in clear Plexiglas cages (25 × 25 × 30 cm) on a 12 h light:dark regime (0730 h–1930 h, light on) at a room temperature of 21 ± 2°C. They were handled daily. All animals had free access to standard food (Hope Farms rat chow) and water. The experiments took place between 0900 h and 1300 h.

Surgery

During surgery the rats were anesthetized with ether. A silicon heart catheter (0.95 mm o.d., 0.50 mm i.d.) was inserted through the right jugular vein externalized on top of the skull according to the technique described earlier (40). This method allows frequent blood sampling in unstressed freely moving rats. For direct recording of arterial blood pressure and heart rate a nonocclusive aortic catheter was implanted (17). The aorta was approached via a midline incision in the abdomen. Blood flow was briefly interrupted by placement of a small artery clip at the level of the iliolumbar vessels. A silicon catheter (0.95 mm o.d., 0.50 mm i.d.) with a J-shaped teflon tip (TW30, Talas, Ommen, The Netherlands), oriented in an upstream direction, was inserted through a 23-gauge needle puncture into the abdominal aorta. This puncture was made approximately 3 mm rostral to the aortic bifurcation. The length of the teflon tubing in the aorta was 1 cm. After insertion, the catheter was anchored inside to the left psoas muscle, just lateral to the aorta. No leakage occurred at the point of insertion, the elasticity of the aortic wall being sufficient to close the opening around the catheter. The arterial catheter was also externalized on top of the skull and filled with a 50% heparinized polyvinylpyrrolidonum (PVP, M = 25,000) solution (40). This PVP was replaced daily with fresh new solution. Eighty-five percent of the catheters were patent after 3 weeks. The rats were given 1–2 weeks to acclimatize to the new cages and recover from surgery.

Cardiovascular Data Acquisition

Arterial blood pressure was recorded via a pressure transducer (Honeywell 130 PC) and an amplifier (E.D.B., Haren, The Netherlands). The heart beat signal was derived from the differentiated blood pressure signal. Both signals were fed into a microcomputer (Olivetti M24). The blood pressure signal was converted analog to digital (12 bits) at a rate of over 1.0 kHz. Data processing and display was performed by the CARDIA software package (Maes, in preparation). HR (beats/min) was determined on a beat-to-beat basis as the reciprocal of individual interbeat intervals. Systolic and diastolic pressures, respectively, were determined as the maximum and minimum pressures observed per interbeat interval. MAP was calculated as (systolic pressure + 2 × diastolic pressure)/3. The program provided an on-line graphical display of HR, and systolic and diastolic pressures. Data were stored on disk automatically.

Blood Sampling and Cardiovascular Monitoring

Before the beginning of the experiments the pressure transducer was calibrated by applying water pressures using the CARDIA program. The connecting tube was filled with heparinized saline (10% heparin of 500 IU/ml). Forty minutes before the start of the experiment the animal's catheters were connected to polyethylene tubes (0.4 m length, 1.45 mm o.d. and 0.75 mm i.d.) for blood sampling and blood pressure/heart rate monitoring in their home cages. After withdrawal of each blood sample (0.45 ml) an equal quantity of donor blood was given to avoid diminution of the blood volume with related changes in hemodynamics (40). Donor blood was obtained from unstressed rats of the same strain with permanent heart catheters.

Chemical Determinations

Blood samples were taken for determination of plasma epinephrine (E), plasma norepinephrine (NE), and plasma corticosterone (CORT) levels. The samples were transferred immediately into chilled (0°C) centrifuge tubes containing 0.01 percent EDTA as antioxidant and 10 μl heparin solution (500 IU/ml) as anticoagulant. They were then centrifuged at 4°C for 10 min at 5000 rpm, and 100 μl of the supernatant were stored at −20°C for CORT and at −80°C for the catecholamine (CA) measurements. Plasma CORT was measured by means of reversed phase high performance liquid chromatography (HPLC), as described earlier (10). Determination of plasma CA concentrations was performed by HPLC in combination with electrochemical detection (23,38).

EXPERIMENT 1

A two-compartment stepthrough apparatus with a sliding door between the compartments (1) was used to investigate the conditioned stress responses in young and in aged rats. The paradigm is similar to the often-used conditioned emotional stress response (CER) paradigm (27), except that only a single footshock was given (one-trial learning). Before the actual measurements started, the rats were briefly placed in a waiting cage adjacent to the apparatus for 1 min. Next, they were trained to enter, from the illuminated platform, the dark compartment where they were left for 5 min. This procedure was repeated three times to allow habituation to occur. During the first test session, which was designed to investigate the effects of transferring and exposing the rats to the apparatus, the rats were transferred directly into the dark compartment, where exploring the environment took most of the time (21). No shock was administered at this time (nonshocked).

Two days later the rats were subjected to the one-trial learning CER paradigm (27). They received a single inescapable scrambled footshock (0.6 mA, AC for 3 s) through the grid floor of the apparatus immediately upon entering the dark compartment of the apparatus (stress chamber). The rats were removed from the dark chamber 30–40 s after termination of the footshock. One day after the inescapable footshock, stress responses were measured during forced exposure to the stress chamber, while no further footshock was administered (shocked). The duration of time spent on immobility behavior was measured at $T = 11$ min up to $T = 13$ min during reexposure to the dark compartment and was used as behavioral parameter. Hormonal and cardiovascular responses were measured in the home cage (at $T = 0$ and $T = 5$ min), during the first and fifth min of exposure to the stress chamber ($T = 10$ and $T = 14$ min) and after return in the home cage ($T = 25$).

EXPERIMENT 2

Two days after Experiment 1 the rats were subjected to the shock probe/conditioned defensive burying (CDB) test. The test

was performed in each individual's home cage in order to avoid disturbance of the neuroendocrine and cardiovascular system by intercage transfer (10,22). A removable teflon probe (6.5 cm long, 1 cm in diameter) was inserted 2 cm above the bedding material (wood shavings) through a small hole in the center of the front wall of the Plexiglas cage. An electric current was passed through two exposed wires (0.5 mm in diameter) each wrapped independently 25 times around the probe. On the first day the shock probe was inserted for 15 min. When touching the probe the animal received a shock of 2 mA/contact. During the entire period the shock circuit was left on [repeated shock probe procedure; Treit and Fundytus (42)]. On the second day the procedure was identical except that no electrical current was applied to the probe. Thus, the procedure investigated the conditioned consequence of former punishment rather than the direct effect of shock. The behavior of each rat was recorded on videotape. The amount of time spent on defensive burying [i.e., moving toward the probe and spraying or pushing the bedding material toward the probe with rapid movements of the snout or forepaws as described earlier by Pinel et al. (32)] was measured during the first 5 min of presentation of the nonelectrified probe on the second day. Blood pressure, heart rate, and hormonal levels were measured for 1-min periods without probe ($T = 0$ and $T = 5$ min), during ($T = 6$, $T = 10$, and $T = 20$ min), and after presentation of the nonelectrified probe ($T = 50$ min).

Statistics

Results are presented as mean ± SEM. Behavioral data were analyzed with the Mann–Whitney *U*-test. For statistical analysis of hormonal and cardiovascular basal values between young and aged animals the two tailed *t*-test (STATS) was used. This test was also used for analysis of the (stress) responses—i.e., peak level minus basal level. The paired *t*-test (STATS) was used for comparisons within subjects. Multivariate analysis of variance with repeated measures (MANOVA) and the Pillai test of SPSS/PC+ were used for multivariate statistics. A probability level of $p < 0.05$ was taken as significant.

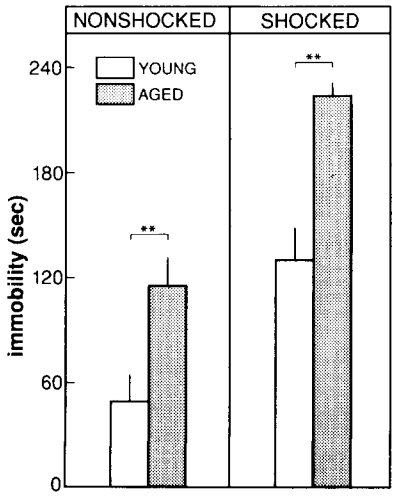

FIG. 1. Immobility behavior of previously nonshocked (24 h earlier) and shocked animals both in aged (24-month-old) and young (3-month-old) animals during reexposure to the stress chamber. Mean ± SEM are from circa 9–10 rats per group. **, $p < 0.01$. (Mann–Whitney *U*-test).

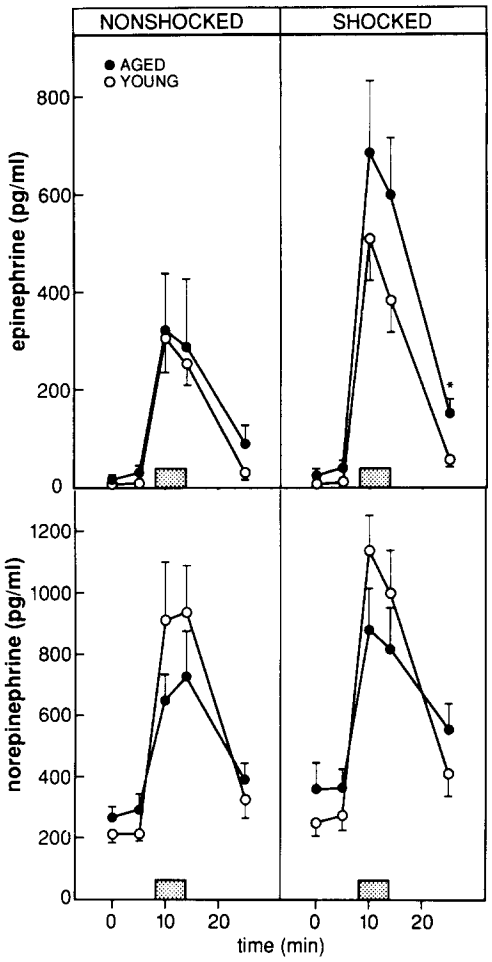

FIG. 2. Plasma levels of epinephrine and norepinephrine of young —○— (3-month-old) and aged —●— (24-month-old) rats before (nonshocked) and 1 day after inescapable shock (shocked). Hormone levels were measured in the home cage, in the experimental room with stress chamber (indicated by the shaded area on the horizontal axis), and after return into the home cage. Data are expressed as the mean ± SEM from circa 9–10 animals in both groups. *, $p < 0.05$ (two-tailed *t*-test). Results from MANOVA of plasma E data are as follows: 1) nonshocked: period effect, $F(4,13) = 4.07$, $p = 0.024$; and 2) shocked: period effect, $F(4,14) = 18.43$, $p < 0.001$. Results from MANOVA of plasma NE data are as follows: 1) nonshocked: period effect, $F(4,13) = 19.84$, $p < 0.001$; and 2) shocked: period effect, $F(4,14) = 26.68$, $p < 0.001$.

RESULTS

EXPERIMENT 1

Behavioral Response in the One-Trial Learning CER Paradigm

Figure 1 shows the behavioral response of the young and the aged rats during reexposure to the shock compartment. The conditioned emotional stress of fear for repetition of the shock elicited an increase in the time spent immobile in both young and aged rats compared to nonshocked controls. The aged animals, whether in the nonshocked or the shocked state, displayed more immobility relative to corresponding young controls ($p < 0.01$).

Catecholamines

Figure 2 shows the basal plasma E and NE levels. The levels did not significantly differ between young and aged rats. Trans-

ferring and exposing animals to the test chamber in the nonshocked trial led to similar elevations of plasma levels of E in both age groups. Both young and aged animals, however, showed a larger E increment one day after shock than in the nonshock trial ($p < 0.05$). Plasma levels of E in aged rats remained elevated above baseline levels in the home cage at $T = 25$ min after exposure to the emotional stressor ($p < 0.05$). NE elevations were apparent in both nonshocked and shocked animals. The aged rats exhibited a diminished NE response (from $T = 5$ to $T = 10$ min) to the emotional stressor compared to young rats ($p < 0.05$). Significant results of the MANOVAs are shown in the legends.

Corticosterone

Figure 3 shows the changes in plasma CORT levels before and 1 day after inescapable electrical footshock in the young and in the aged rats. Basal plasma CORT levels tended to be higher in the nonshocked aged rats compared to the young controls, but the differences were not significant. Transferring and exposing the animals to the test chamber led to equivalent increases in plasma levels of CORT in both young and old rats. Shocked animals of both ages showed a further increase of the CORT response compared to the nonshocked controls ($p < 0.05$). One day after shock, the plasma CORT levels of aged rats in the home cage were significantly higher than these of the young controls ($p < 0.05$). In the stressed condition, both groups reached the identical peak plasma CORT levels at $T = 25$ min. Only significant results of the MANOVAs are shown in the figure legends.

Cardiovascular Measurements

Figure 4 shows the MAP (in mmHg) and HR (beats/min) before, during, and after exposure to the dark test chamber in the young and in the aged rats before (nonshocked) and 1 day after inescapable shock (shocked). The basal MAP of the aged rats was significantly higher (at least $p < 0.05$), whereas the basal HR was significantly lower ($p < 0.05$) in both the nonshocked and the shocked state compared to young animals. Transferring and exposing the animals to the test chamber caused an increase of both HR and MAP. There was no significant difference in the responsiveness of the cardiovascular system in nonshocked and shocked animals, but a tendency to diminished responsiveness was observed in the aged animals. Significant results of the MANOVAs are shown in the figure legends.

EXPERIMENT 2

Behavioral Response in the CDB Test

One day after the shock both young and aged rats spent roughly the same amount of time (163 ± 23 s, $n = 8$; 150 ± 25 s, $n = 9$; respectively) on defensive burying, i.e., pushing of bedding material toward or over the nonelectrified probe during the first 5 min of presentation of the probe.

Catecholamines

Figure 5 shows the plasma E and NE levels before, during, and after presentation of the nonelectrified probe 1 day after shock. There was practically no E response to the presentation of the probe in both the aged and the young animals. Basal plasma NE levels tended to be higher in the aged animals, but this difference was not significant. During presentation of the probe the NE levels showed a larger increase in young than in aged rats, but these failed to reach the level of significance.

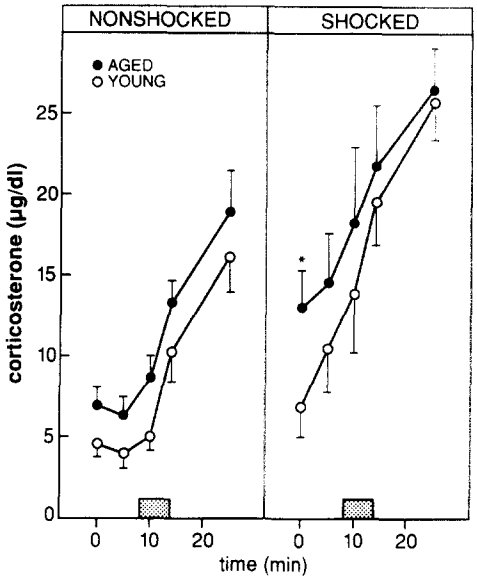

FIG. 3. Plasma corticosterone levels of young — ○ — (3-month-old) and — ● — aged (24-month-old) rats before (nonshocked) and 1 day after inescapable shock. Hormone levels are measured in the home cage, the experimental room with stress-chamber (indicated by the shaded area on the horizontal axis), and after return into the home cage. Data are expressed as mean ± SEM from circa 9–11 animals in both the young and the aged group. *, $p < 0.05$ (two-tailed t-test). Result from MANOVA of plasma CORT data are as follows: 1) nonshocked: period effect, $F(4,16) = 14.16$, $p < 0.001$; and 2) shocked: period effect, $F(4,15) = 26.22$, $p < 0.001$.

Corticosterone

There was no significant difference in the plasma CORT levels between the aged and the young rats before, during, or after presentation of the nonelectrified probe (Fig. 6). Plasma CORT increases were of the same order of magnitude in both age groups.

Cardiovascular Measurements

Figure 7 shows the MAP and HR before, during, and after presentation of the nonelectrified probe in the home cage of the young and the aged rats. The systolic and diastolic pressure in the aged animals was respectively 142 ± 7 mmHg and 108 ± 8 mmHg. In the young animals systolic pressure was 127 ± 4 mmHg and diastolic pressure was 84 ± 2 mmHg. During all measurements, MAP of the aged animals was significantly higher ($p < 0.01$ or $p < 0.05$, respectively), whereas HR in the aged group was significantly lower compared to young animals ($p < 0.05$ or $p < 0.01$, respectively). The MAP response due to presentation of the nonelectrified probe was in the same order of magnitude in young and aged rats, whereas the HR response of aged relative to young animals was less and approached significance ($p = 0.07$).

DISCUSSION

In the present study the differences between 3-month- and 24-month-old male Wistar rats in physiology and behavior during and after exposure to conditioned emotional stressors were investigated. Aging affected the basal activity of the cardiovascular system. Aged rats that had absence of control (in the CER paradigm) showed elevated basal plasma levels of CORT, diminished plasma NE responses, and a delayed post-stress recovery of plasma catecholamines compared to young controls.

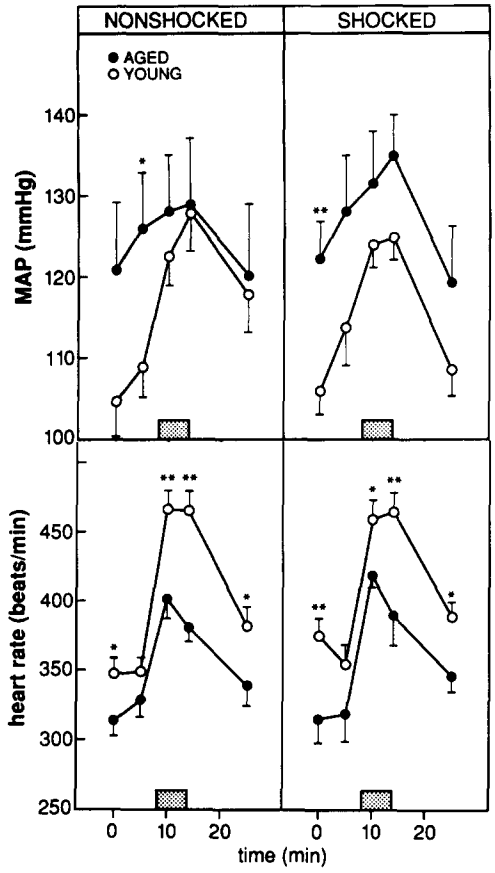

FIG. 4. Mean blood pressure (MAP) and heart rate (HR in beats/min) of young — ○ — (3-month-old) and aged — ● — (24-month-old) rats before (nonshocked) and 1 day after inescapable shock (shocked). HR was measured in the home cage, the experimental room with stress chamber (indicated by the shaded area on the horizontal axis), and after return to the home cage. Data are expressed as mean ± SEM from circa 8–10 animals in both the aged and young group. *, $p < 0.05$; **, $p < 0.01$ (two-tailed t-test). Results from MANOVA of MAP data are as follows: 1) nonshocked: period effect, $F(4,11) = 29.4$, $p < 0.001$; period × aging, $F(4,11) = 7.96$, $p = 0.003$; and 2) shocked: period effect, $F(4,13) = 31.86$, $p < 0.001$. Results from MANOVA of heart rate data are as follows: 1) nonshocked: aging effect, $F(1,14) = 16.71$, $p = 0.001$; period effect, $F(4,11) = 25.15$, $p < 0.001$; and 2) shocked: aging effect, $F(1,16) = 12.32$, $p = 0.003$; period effect, $F(4,13) = 26.27$, $p < 0.001$.

Rats were in succession tested in the conditioned emotional stress (CER) paradigm in which immobility was displayed and in the conditioned defensive burying (CDB) test in which animals showed behavioral activity. The behavioral responses in the aged animals in both test conditions were fully maintained which is in accordance with earlier findings (31,41). This suggests that there was neither learning nor memory impairment for the conditioned stimuli. The significantly higher score of immobility in the aged relative to the young animals is in agreement with findings of a decreased spontaneous locomotor activity in aged animals (44).

The stress response in the CER paradigm was characterized by passive behavior (immobility) associated with increased plasma levels of corticosterone (CORT) and epinephrine (E). Thus, simultaneous activation of both the adrenomedullary system and the pituitary-adrenocortical axis appear to have occurred. Findings by Kvetnansky et al. (24,25) and De Boer et al. (10,11) support this conclusion. In the CDB paradigm rats displayed active coping behavior (defensive burying) with concomitant rise in mean arterial pressure (MAP) and heart rate (HR), and increases in plasma levels of CORT and norepinephrine (NE). These results are in accordance with the findings that physical activity causes an increase in the release of NE (37). Furthermore, these results fit in well with the view that the pituitary-adrenocortical axis can be regulated independently from the sympathoadrenomedullary system (10,24,25). High plasma NE levels in combination with low plasma levels of E suggests that a dissociation of central regulation of the peripheral sympathetic nerves and the adrenal medulla seems to have occurred during the present testing conditions (10,24,25,37,45). An increase in sympathoadrenal activity implies enhanced outflow of catecholamines from the adrenal medulla and the peripheral nerve endings of the sympathetic nervous system. However, plasma levels of NE investigated in young animals depend on release, reuptake, metabolic, and excretory processes (5). Therefore changes in plasma NE levels should be interpreted with caution. In general, venous plasma NE provides a useful estimation of average peripheral sympathetic outflow. Plasma levels of NE and E are increased during many types of acute stress and physical activity (7,10,30). Recently, it was reported that physical activity in young rats selectively caused an increase in the release of NE. Activation of the adrenal medulla was evoked by emotional stressors and led to an increase in E levels in the

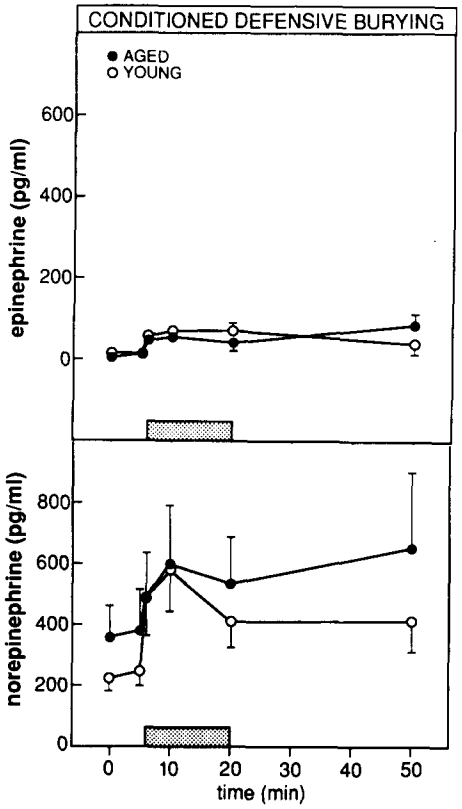

FIG. 5. Plasma levels of epinephrine and norepinephrine in young — ○ — (3-month-old) and aged — ● — (24-month-old) rats before, during, and after presentation of the nonelectrified shock probe in the rat's home cage 1 day after shock. The period of probe presentation is indicated by the shaded area on the horizontal axis. Data are expressed as mean ± SEM from nine animals per group. The t-tests and MANOVAs revealed no significant differences.

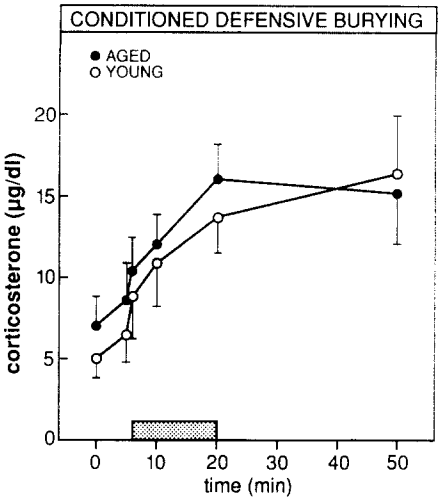

FIG. 6. Plasma levels of corticosterone of young — ○ — (3-month-old) and aged — ● — (24-month-old) rats before, during, and after presentation of the nonelectrified shock probe in the rat's home cage one day after shock. For further explanations see Fig. 5. Data are expressed as mean ± SEM from 10 animals in the young group and from nine in the aged group. The *t*-tests revealed no significant differences. Results from MANOVAs of plasma CORT data are as follows: period effect, $F(4,14) = 11.86$, $p < 0.001$.

blood (37). It cannot be excluded that earlier stress experience in the CER paradigm has influenced the results of the exposure to the CDB paradigm.

The effect of aging on the basal catecholamine levels seems rather complex. In aged rats the resting levels of plasma NE tended to be higher, whereas the basal levels of E were unchanged. Increased plasma basal levels of NE have been reported in aged rats (7,36, Buwalda et al., submitted). Elevated levels of plasma NE may reflect an age-related increase of NE spillover rate (36). Factors such as a decrease in the metabolic clearance rate cannot be excluded (16). Therefore it is questionable whether the NE levels in the aged animals reflect a different pattern of NE release and altered sympathetic nerve activity. The possible mechanisms by which aging could produce an increase in sympathetic nerve activity e.g., by a decrease in central vagal inhibitory mechanisms (31), an increase in central excitatory mechanism, or through a decrease in baroreceptor sensitivity (16), are presently subject to further investigations.

The effect of aging on the plasma E and NE responses in the aged animals was different compared to the young animals in the CER paradigm. Following exposure to the emotional stressor, aged rats exhibited a smaller plasma NE response, whereas poststress return to basal catecholamine levels seemed to be delayed. The density of nerve terminals may decline in the heart and in some arteries with aging (2,8). This could explain why the release of plasma NE in stressed aged rats is reduced. The slower return of plasma E to prestress values in these animals is in agreement with other studies in the rat (30). Additional research with regard to the clearance of E and NE from the blood would be especially useful.

Basal plasma corticosterone (CORT) levels showed a tendency to increase with age, and basal CORT levels of the aged animals were significantly elevated 1 day after footshock. Elevated basal plasma levels of CORT in the aged rats is in agreement with a number of other reports (4,28,35). This age-dependent difference may be related to specific corticoid receptorbound brain processes (12,13,19,26,33,34) or changes in adrenal sensitivity to ACTH (8).

The effects of aging on the cardiovascular system were pronounced. In our study basal MAP values were elevated in aged rats while basal HR values showed a decrease. Conflicting data exist for MAP and HR in freely moving aged rats. An increased basal MAP in 20–24-month-old animals was reported by Chiuch et al. (7), and a nonsignificant elevation by McCarty (30). Some investigators have reported higher systolic blood pressure (39), while others failed to observe changes in diastolic blood pressure (15). The finding that resting HR declines with age is consistent with one study (7), while in conflict with others that report no change (15) or an increase in HR in aged rats (30). The lower HR of the aged animals in the present study may be due to a lower intrinsic HR of the aged animals (Buwalda et al., submitted). Possible factors in causing these different findings may be the use of different rat strains or the consequences of differences in previous stress history or rearing conditions of the animals. Another possible reason for different findings within the

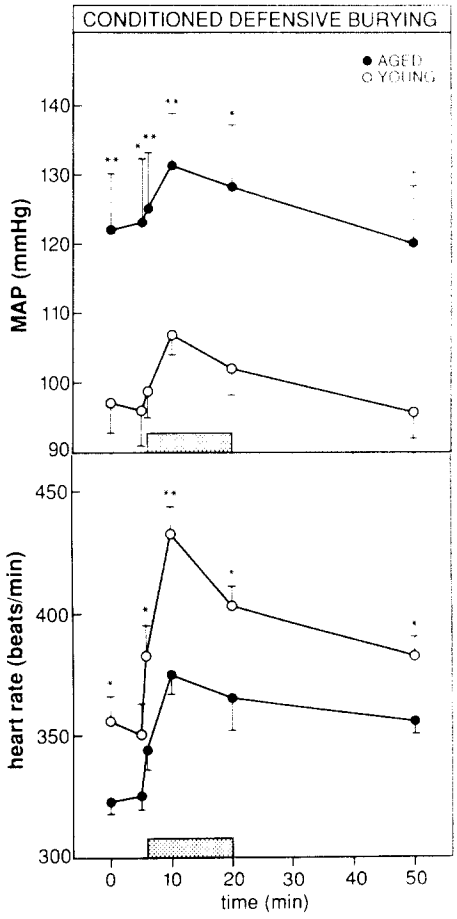

FIG. 7. Mean arterial pressure (MAP in mmHg) and heart rate (beats/min) of young — ○ — (3-month-old) and aged — ● — (24-month-old) rats before, during, and after presentation of the nonelectrified shock probe in the rat's home cage one day after shock. For further explanations see Fig. 5. Data are expressed as mean ± SEM from 9 animals in the young group and from 8 animals in the aged group. *, $p < 0.05$; **, $p < 0.01$ (two-tailed *t*-test). Results from MANOVAs of MAP data are as follows: aging effect, $F(1,15) = 5.54$, $p = 0.033$; period effect, $F(5,11) = 4.87$, $p = 0.014$. Results from heart rate data are as follows: aging effect, $F(1,15) = 10.49$, $p = 0.006$; period effect, $F(5,11) = 12.89$, $p < 0.001$.

same laboratory may be that a group of aged animals is more heterogeneous than a group of young animals, as reflected in the larger SEM.

In both paradigms the tachycardia is of the same magnitude in the young and the aged animals. Borton and Docherty (6) suggested that a reduced function of neuronal uptake of NE in the aged rat may serve to maintain responses in spite of a reduced postjunctional responsiveness in the heart. The MAP response due to activation or emotional stressors was not significantly different between the aged and the young animals.

Due to the small amount of data no reliable correlations could be made between hormonal and cardiovascular values. It remains a matter of discussion whether elevated basal MAP levels are associated with an increase in arterial stiffness or elevated levels of catecholamines. However, a role of catecholamines in the development of age-related hypertension cannot be excluded (29,30). It is tempting to suggest that once hypertension has been established, the elevated MAP may accelerate the rigidity of large arteries that develops with age (26). Longitudinal studies will be necessary for a deeper understanding of cause and effect. Furthermore, the social status of the animals (dominant, subdominant, subordinate, or outcast) should be taken into account.

In summary, aged rats that have been exposed to the CER paradigm showed diminished plasma NE responses. In those aged animals, levels of E remained elevated to a greater extent during recovery from stress compared to young animals. No significant differences were seen in the neuroendocrine measurements of young and aged animals in the CDB paradigm in which the animals display active behavior. Furthermore, aging may affect the cardiovascular system which is reflected in a higher basal MAP and lower basal HR in the aged animals. In spite of these age-induced differences, the behavioral response was preserved in both actively and passively behaving aged animals. It is suggested that the age-related differences in neuroendocrine and autonomic parameters are more clearly apparent in stressed animals during absence of control (immobility) than during active control (defensive burying).

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