# *SUSTAINED EFFECTS OF BRIEF DAILY STRESS (FIGHTING) UPON BRAIN AND ADRENAL CATECHOLAMINES AND ADRENAL, SPLEEN, AND HEART WEIGHTS OF MICE**

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*Communicated by Seymour S. Kety, June 23, 1969*

*Abstract.*—Male white Swiss mice that had previously been made aggressive by several weeks of individual housing were allowed to fight for 5 to 10 minutes each day for 5, 10, or 14 consecutive days; fighting caused a marked enlargement of their adrenals, spleens, and hearts, and a large increase in adrenal catecholamines; brain catecholamines were slightly increased. Long-term group caging, under conditions where the mice did not fight, caused changes that were directionally the same but of smaller magnitude. Similar sociophysiological influences may be important in natural populations. Fighting mice, used under well-defined and closely controlled conditions, may be useful for studying normal mechanisms of neuroendocrine adaptation and control, and, possibly, for studying some forms of hypertension and cardiovascular-renal disease.

Brief stressful experiences, either physical or emotional, may have profound long-lasting physiological effects.[1-12] We have studied certain aspects of these effects by allowing male mice, previously made aggressive by long-term isolation, to fight for only 5 to 10 minutes on one occasion each day for 5, 10, or 14 consecutive days. These short daily periods of natural stress increased the weight of the adrenal, spleen, and heart, caused modest increases in catecholamine concentrations in the brain, and markedly increased catecholamines in the adrenal medulla.

*Methods.*—Two fighting experiments were conducted using male white Swiss mice that were made aggressive by housing them individually for a number of weeks subsequent to weaning. They were kept in a quiet room containing no females and no other species of animal. In the first experiment, DUB/ICR mice (Dublin Laboratory Animals, Dublin, Va.) were housed either individually or in groups of eight for approximately 4 months, after which half of the isolated mice were placed together and allowed to fight for 10 min each day for 14 days. In the second experiment, "Specific Pathogen Free" CD-1 mice (Charles River Breeders, Wilmington, Mass.) were housed individually for approximately 2 months, after which they were either left undisturbed in their individual cages as controls or placed together and allowed to fight for only 5 min daily for either 5 or 10 consecutive days before sacrifice. The mice were housed in polycarbonate cages 7 × 11 × 5 inches in size. Their diet was unmodified Wayne Feed for Laboratory Mice. In order to avoid extraneous disturbances, the cages were not changed for any of the mice during the 5 to 14 day experimental periods. The mice fought in pairs in a cage strange to both mice, except that in the few instances when they failed to fight in pairs they were placed into groups of four in order to assure that they would be involved in fighting. The mice were randomly paired and, hence, were not with the same partner from one fighting period to the next.

All mice were killed by decapitation 24 hr after the last fight. They were killed between 8:00 P.M. and 11:00 P.M., and a strict rotation was maintained between treatments in all manipulations in order to minimize the biasing effects of normal diurnal variations in biogenic amines. The brain, spleen, heart (ventricles only), left adrenal, and left kidney were removed from each animal, trimmed in a consistent manner, weighed on a roller torsion balance, and frozen on dry ice. Individual whole brains were later analyzed for norepinephrine, dopamine, and serotonin,[13] and the adrenal was analyzed for norepinephrine and epinephrine.[14] The spleen, heart, and kidney were dried for 24 hr in an oven at 90°C and weighed again. The data were analyzed by analysis of variance.

*Results.*—When mice that previously had been individually caged were paired, they began fighting within a minute and they fought intensely, with only short breaks, for most of the time spent together. The intensity of their fighting diminished with repeated daily exposure. A quantitative estimate of this decrement was obtained by comparing the intensity of fighting by mice on their fourteenth consecutive day of fighting exposure with that of control mice that were fighting for the first time; the control mice had been weaned within the same 2 to 4 day period and had been maintained in the same room under identical conditions of individual housing, except that they had not been allowed to fight. The fighting observations of the two sets of mice were made concurrently. Tissues were not taken from the mice that fought only once, and they were used for no other purpose than this comparative study of fighting. Table 1 shows

TABLE 1. *Decrement in fighting with repeated exposure.**

| | First exposure | 14th daily exposure |
|---|---|---|
| Number of pairs constituted | 16 | 16 |
| Number of pairs actually fighting | 16 | 11 |
| Latency of first fight (sec) | 88 ± 11 | 137 ± 26† |
| Number of fights/5 min | 81 ± 8 | 26 ± 6‡ |

* Mice were paired in a strange cage. The latency of the first attack and the number of definitive biting contacts occurring in the succeeding 5 min were estimated using a stopwatch and a mechanical counter. Values are means ± SEM.
† $p < 0.05$ (Wilcoxon two-sample test).
‡ $p < 0.001$ (Student's $t$-test).

that fewer mice fought on the fourteenth exposure than on the first (69 vs. 100%), that the latent period for the commencement of fighting was longer, and that they fought less intensely. Blood was seldom drawn in the fighting. The wounds that did occur were superficial and were located mostly on the tail and rump. No fighting was observed among the group-housed mice, and they bore no scars.

Figures 1 and 2 graphically present the tissue weight and chemical content data from the two experiments. The changes that were found are plotted as percentage increases or decreases in wet tissue weights or in tissue amine concentrations in experimental as compared with undisturbed isolate control mice. The actual data from these two experiments, and also the dry weights of the hearts, spleens, and kidneys, are given in Table 2.

Daily fighting for either 10 days or 14 days caused a significant elevation (10%) in whole brain levels of dopamine. Whole brain norepinephrine was elevated to the same degree, but only after 14 days. There were no significant differences in whole brain serotonin.

In the adrenal medulla, norepinephrine was not different for mice that had been housed from the time of weaning in group versus individual cages. However, daily fighting produced large elevations in the level of norepinephrine in the adrenal medulla, i.e., 85, 108, and 67 per cent, respectively, after 5, 10, and 14 days.

The adrenal epinephrine content was significantly greater (36%) in grouped than in isolated mice. After only five days of fighting it was not elevated; but after 10 and 14 days of fighting, respectively, it was elevated 63 and 56 per cent.

Although body weights were similar for all mice, adrenal and spleen weights of mice that fought for 5 to 10 minutes daily were considerably larger than those of mice that lived undisturbed in individual cages; adrenals and spleens of grouped mice were intermediate in weight between these two extremes. Grouped mice had adrenals that were 20 per cent larger and spleens that were 68 per cent larger than undisturbed individually housed mice. However, individually housed mice that were allowed to fight daily for 14 days had adrenals and spleens that were, respectively, 17 and 22 per cent heavier than those of the mice that lived together in groups, and 40 and 105 per cent heavier than controls.‡

Kidneys of mice that had lived in groups for four months were significantly smaller (10%) than those of individually housed mice. However, repeated exposure to fighting over the relatively short time periods employed in these experiments had no significant effect upon kidney weight.

Heart ventricle weights were virtually identical in mice that lived compatibly

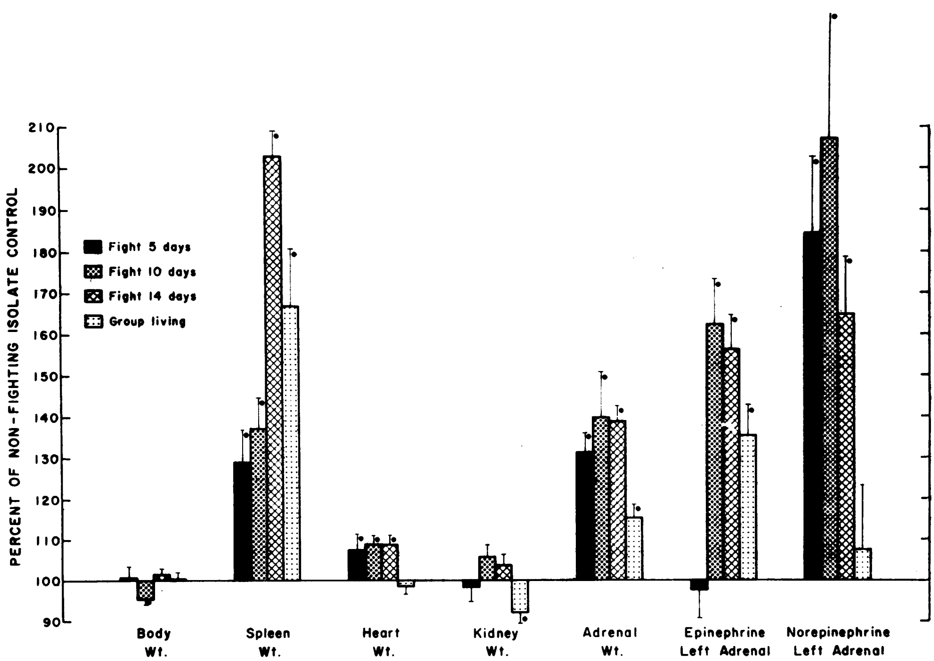


FIG. 1.—Effect upon tissue weights and adrenal catecholamines of permitting individually housed male mice to fight for 5–10 min daily, as compared with undisturbed group-housed and individually housed mice. Each mean and SEM. is presented as a percentage of the nonfighting isolate control mean. Black dots indicate individual means that differ significantly from controls (at least $p < 0.05$ by two-tailed $t$-test). The data for the two experiments that are combined in this figure are given in detail in Table 2.

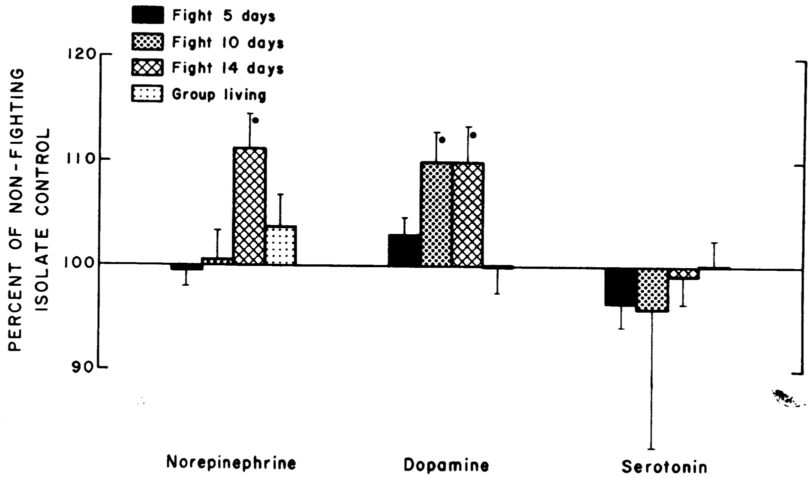


FIG. 2.—Effect upon whole brain catecholamines of permitting individually housed male mice to fight for 5–10 min daily as compared with undisturbed group-housed and individually housed mice. Each mean and SEM. is presented as a percentage of the nonfighting isolate control mean. Black dots indicate individual means that differ significantly from controls (at least $p < 0.05$ by two-tailed $t$-test). The data for the two experiments that are combined in this figure are given in detail in Table 2.

in the same group from the time of weaning as in their undisturbed individually housed littermates. However, daily bouts of fighting for either 5, 10, or 14 days caused significant increases (10–12%) in the weight of the ventricles.

*Discussion.*—Other investigators have also found elevated brain catecholamine levels in laboratory rodents 24 hours after the last of several short daily periods of stress. Kety *et al.*[4] showed this effect for norepinephrine in the brains of rats that had been given electroconvulsive shock (ECS) twice a day for seven days. Thierry *et al.*[12] found rat brain norepinephrine elevated 24 hours after three days of repetitive stress. And Nielson and Fleming[5] found both brain norepinephrine and dopamine elevated in rats after daily ECS or cold stress. Therefore, our observations made on mice that had been exposed to the natural stress of fighting for 5 to 10 minutes daily for 5 to 14 days are consistent with these other reports. Together, these experiments clearly demonstrate that intense stress of short duration has sustained effects upon brain catecholamines. Since the acute effect of intense fighting may be to *lower* norepinephrine and dopamine, at least in the brainstem,[14] it seems apparent that these elevated amine levels reflect adaptive compensations of some kind. However, the nature of these adaptive changes and their relative importance in different parts of the brain remain to be determined.

Eleftheriou and Church[15] have found both elevations and reductions in brain norepinephrine, depending upon the number of days of fighting exposure, for mice that were exposed to trained fighters for 2 to 5 minutes/day for 2, 4, 8, and 16 days, and they also found serotonin to be reduced in some parts of the brain. However, since Eleftheriou and Church killed their mice 20 minutes

TABLE 2. *Changes in brain and adrenal catecholamines and in body and tissue weights*

| | Expt. 1 (Fight 14 days, 10 min/day) | | | | | |
|---|---|---|---|---|---|---|
| | Control isolates not-fight | Pre-isolate fight | Group-living not-fight | F ≠ CI | $p<$ F ≠ Gp | CI ≠ Gp |
| No. of mice | 34 | 34 | 34 | | | |
| Body weight (gm) | 36 ± 0.5 | 36 ± 0.5 | 36 ± 0.6 | — | — | — |
| Whole brain (mg) | 465 ± 3.2 | 472 ± 2.9† | 463 ± 3.8 | 0.09 | 0.07 | — |
| Norepinephrine (ng/gm) | 419 ± 9.1 | 466 ± 15.2 | 435 ± 13.8 | 0.01 | — | — |
| Dopamine (ng/gm) | 771 ± 16.4 | 851 ± 25.4 | 771 ± 19.7 | 0.01 | 0.02 | — |
| Serotonin (ng/gm) | 922 ± 32.4 | 914 ± 25.0 | 923 ± 23.3 | — | — | — |
| Left adrenal (mg) | 2.0 ± 0.05 | 2.8 ± 0.07 | 2.4 ± 0.07 | 0.001 | 0.001 | 0.001 |
| Epinephrine (μg) | 3.6 ± 0.15 | 5.6 ± 0.30 | 4.9 ± 0.26 | 0.001 | 0.05 | 0.001 |
| Norepinephrine (μg) | 1.5 ± 0.13 | 2.5 ± 0.21 | 1.6 ± 0.24 | 0.001 | 0.005 | — |
| Spleen, wet (mg) | 105 ± 4.5 | 215 ± 7.0 | 176 ± 14.8 | 0.001 | 0.025 | 0.001 |
| " dry (mg) | 22 ± 1.0 | 45 ± 1.5 | 38 ± 3.3 | 0.001 | 0.06 | 0.001 |
| Heart, wet (mg) | 158 ± 2.3 | 172 ± 3.5 | 155 ± 2.8 | 0.005 | 0.001 | — |
| " dry (mg) | 34 ± 0.5 | 37 ± 0.7 | 33 ± 0.6 | 0.001 | 0.001 | — |
| Left kidney, wet (mg) | 276 ± 6.5 | 287 ± 6.3 | 254 ± 6.2 | — | 0.001 | 0.025 |
| " " dry (mg) | 59 ± 1.4 | 61 ± 1.5 | 54 ± 1.1 | — | 0.001 | 0.025 |

* Each value is a mean ±SEM. Before commencing fighting, mice had been housed post-weaning individually or in groups for 3 mos (expt. 1) or individually for 2 mos (expt. 2). The mice fought in pairs in a cage strange to both mice. Differences were evaluated by Student's $t$-test (two-tailed).

after the last exposure to fighting whereas we killed ours 24 hours after the last exposure, and since acute fighting itself causes rapid biphasic changes in brain amines that are dependent upon the intensity of fighting,[16] our experiments and theirs cannot be directly compared.

Animals that live under the relatively low stimulus conditions of individual housing have lower basal levels of adrenalcortical activity than animals that live in groups.[9, 10, 30, 31] However, they are hyperexcitable, presumably because they maintain a low level of tonic cortical inhibition of subcortical activating systems;[17, 30, 32] disturbing them causes exaggerated elevations of plasma corticosterone, and the levels remain high for hours after a single short-lasting disturbance.[10] Since short episodes of daily fighting previously have been shown to elevate plasma corticosterone,[9] to enlarge the adrenals of mice,[8, 9] and to produce distinct histological changes in the adrenals of rats,[3] the dramatic enlargements that we found to be caused by fighting almost certainly reflect a sustained activation of the anterior pituitary-adrenal cortical axis.§

Grouped mice secrete adrenal epinephrine at higher basal rates than undisturbed individually housed mice.[18] Hence, as we have previously suggested, the elevated levels of epinephrine that are commonly found in the adrenals of grouped mice[17, 18, 30] probably represent an adaptation to this increased release and utilization. Likewise, since an acute episode of intense fighting drastically depletes adrenal epinephrine[14] (by 45% within 60 min), the large increases in adrenal catecholamines that were found 24 hours after repeated daily exposure to fighting in the experiments reported here probably indicate that the adrenal medulla had undergone adaptive changes in its capacity for synthesis and storage. The relative time dynamics for the elevation of adrenal medullary norepinephrine and epinephrine that we observed agree with reports of earlier investigators that norepinephrine is replenished a great deal more rapidly than epinephrine in exhausted adrenals.[19]

*produced by fighting briefly once each day.**

| Expt. 2 (Fight 5 or 10 days, 5 min/day) | | | | | |
|---|---|---|---|---|---|
| Control isolates not-fight (CI) | Pre-isolate fight 5 days (5) | Pre-isolate fight 10 days (10) | $p<$ CI ≠ 5 | $p<$ CI ≠ 10 | $p<$ 5 ≠ 10 |
| 11 | 12 | 11 | | | |
| 38 ± 0.6 | 38 ± 1.0 | 36 ± 0.5 | — | 0.02 | — |
| 498 ± 4.8 | 504 ± 6.2 | 512 ± 6.0† | — | 0.06 | — |
| 341 ± 8.5 | 338 ± 6.2 | 343 ± 9.2 | — | — | — |
| 733 ± 31.9 | 755 ± 12.3 | 808 ± 20.7 | — | 0.05 | 0.05 |
| 612 ± 18.0 | 590 ± 13.3 | 587 ± 8.1 | — | — | — |
| 1.9 ± 0.12 | 2.5 ± 0.09 | 2.6 ± 0.21 | 0.001 | 0.005 | — |
| 4.0 ± 0.28 | 3.9 ± 0.28 | 6.5 ± 0.45 | — | 0.001 | 0.001 |
| 1.3 ± 0.06 | 2.4 ± 0.24 | 2.7 ± 0.41 | 0.001 | 0.001 | — |
| 109 ± 4.5 | 141 ± 8.7 | 150 ± 8.0 | 0.001 | 0.001 | — |
| 22 ± 1.0 | 30 ± 1.8 | 31 ± 1.4 | 0.001 | 0.001 | — |
| 158 ± 4.4 | 170 ± 5.7 | 172 ± 3.6 | — | 0.02 | — |
| 34 ± 0.7 | 37 ± 1.2 | 38 ± 0.7 | 0.05 | 0.005 | — |
| 333 ± 10.1 | 327 ± 11.9 | 353 ± 9.7 | — | — | — |
| 71 ± 2.4 | 71 ± 2.7 | 75 ± 2.0 | — | — | — |

† Combined brain weights of the 10-day and 14-day fighting mice vs. combined brain weights of their controls are different ($t = 2.39$, $p < 0.02$).

Wurtman and Axelrod[20] have shown that glucocorticoids are necessary for the production of phenylethanolamine-*N*-methyltransferase (PNMT), the adrenal medullary enzyme that mediates the methylation of norepinephrine by *S*-adenosylmethionine to form epinephrine. They found that levels of PNMT and also epinephrine dropped after hypophysectomy and returned to normal after the administration of exogenous glucocorticoids or ACTH, although administering ACTH to normal animals did not cause supranormal elevations of adrenal epinephrine. Recently, however, Vernikos-Danellis *et al.*[21] reported that pituitary tumor transplants in rats caused a 160 per cent increase in adrenal epinephrine, and they suggested that under appropriate conditions stimulation of adrenal cortical activity in normal nonhypophysectomized animals might cause an adaptive increase in the production of epinephrine by the adrenal medulla. The marked increases in epinephrine levels that occurred concomitant with a 32–40 per cent increase in adrenal weight in our experiments would be consistent with this speculative suggestion. The marked elevation of adrenal norepinephrine that we observed could reflect an increased tyrosine hydroxylase activity such as that recently reported by Thoenen *et al.*[22] However, enzyme activities have not yet been assayed in the adrenals of our fighting mice.

Enlargement of the spleen as a consequence of periodic fighting, and of group housing, has also been previously reported[6] and, histologically,¶ it has been said to reflect an increased extramedullary hematopoiesis.[23]

Blood pressures of our mice that live in groups have been measured and reported by Henry *et al.*;[24] grouped mice were found to have blood pressures that were somewhat higher at an advanced age than those of individually housed mice, even when the groups had been constituted at weaning so that there was little to no detectable fighting. Under the latter conditions, which are similar to those employed for the grouped animals in the experiments reported here, the heart is not necessarily enlarged but the kidney is contracted[17] and often shows clear histological evidence of glomerular hyalinization and nephritis with advancing age (in preparation). Shapiro *et al.*[25] have confirmed the observations of Henry *et al.*[24] that crowding causes a mild elevation of blood pressure in mice.

We have previously reported that mice that live in groups, although not necessarily crowded, and also subordinate mice that are frequent recipients of attack by dominants, sometimes have enlarged hearts.[17, 26] Henry *et al.*[24] have recently found that when previously isolated male mice are forced to live together (so that there is a great deal of strife), there is a marked elevation in blood pressure and a 10 per cent enlargement of the heart, together with histological evidence of myocardial fibrosis.¶ Since blood pressure is markedly elevated in male mice that live apart but occasionally come together and fight,[24] elevation in blood pressure may have contributed to the consistent enlargement of the heart that we found in the mice that fought for 5 to 10 minutes per day in the experiments reported here.

We cannot preclude the possibility that the observed cardiac hypertrophy was due simply to the exercise associated with fighting, since it is well known that exercise may enlarge the heart; however the experimental exposures that are required to enlarge the heart by exercise alone are usually of much longer duration than the short periods of fighting employed in our experiments (cf. ref. 27). Neither, however, can we discount the possibility that this cardiac hypertrophy may have resulted from the intense emotional excitation of very hyperexcitable animals. In evaluating the possible relevance of emotional factors, we note that Geber and Anderson[28] produced cardiac hypertrophy in both rats and rabbits simply by subjecting them for three weeks to intermittent noise stress and brightly flashing lights.

The fighting of male mice provides a relatively natural form of physiological stress. It may be useful as a tool for studying normal mechanisms of neuroendocrine adaptation and control, and it may also prove to provide a useful model for studying some forms of hypertension and cardiovascular-renal disease.[7] At least some components of fighting stress are probably psychological, since merely allowing mice to witness fighting among other male mice[29] or to be in the presence of a known aggressor[9] has effects upon brainstem norepinephrine, plasma corticoids, and adrenal weight that are similar to those produced by actually fighting. Hence, it may be possible to use fighting mice, under carefully controlled conditions, to gain a better understanding of the importance of emotional stresses in the pathological processes discussed above.

The growing evidence that very short-lasting social stresses have profound, long-lasting effects upon physiological and behavioral functions strengthens the suggestion that social and population conditions have psychophysiological effects that importantly influence the maintenance of health and the development of mental or physical illness.[3, 30, 31]

* This work was supported by grants from the Air Force Office of Scientific Research (AF-AFOSR-1227-67), the National Institute of Mental Health (MH-13535), and the U.S. Army Medical Research and Development Command (DA-MD-49-193-67-G9232).

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‡ The adrenal weights were reported at the International Symposium on Aggressive Behavior, Milan, Italy, in May, 1968.

§ We should emphasize the technical and interpretive problems that may result from the fact that periodic stressful disturbance of highly excitable isolated mice causes them to have *larger* adrenals than grouped mice, whereas mere isolation without disturbance normally *decreases* adrenal weight. Opposite results may thus be obtained from ostensibly similar experimental designs as a consequence of failure to note periodic disturbance to the animals, and/or to recognize the importance of its effect. This may account for the occasional reports of enlarged adrenals in isolated rodents [A. S. Weltman *et al., Aerospace Med.*, **37,** 804 (1966); E. Geller *et al., J. Neurochem.*, **12,** 949 (1965); A. Hatch *et al., Science*, **142,** 507 (1966); E. B. Sigg *et al., Endocrinol.* **78,** 679 (1966)], which seem to be at variance with the usual findings in this area of investigation.[3, 10, 26, 30–32, 33]

¶ Since the tissues of our fighting mice were used either for chemical assay or for dry weight determinations, no histological studies have yet been made.


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