Pharmacology Biochemistry and Behavior, Vol. 58, No. 4, pp. 881–886, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(97)00053-1

Differential Effects of Immunologic Challenge on Self-Stimulation From the Nucleus Accumbens and the Substantia Nigra

ROBERT M. ZACHARKO, STEVE ZALCMAN, GLENDA MACNEIL, MONIQUE ANDREWS, PAUL D. MENDELLA AND HYMIE ANISMAN

Carleton University, Life Sciences Research Building, Institute of Neuroscience, Ottawa, Ontario K1S 5B6 Canada

Received 13 June 1996; Revised 5 December 1996; Accepted 24 January 1997

ZACHARKO, R. M., S. ZALCMAN, G. MACNEIL, M. ANDREWS, P. D. MENDELLA AND H. ANISMAN. *Differential effects of immunologic challenge on self-stimulation from the nucleus accumbens and the substantia nigra.* PHARMACOL BIOCHEM BEHAV **58**(4) 881–886, 1997.—Paralleling the effects of uncontrollable stressors, systemic administration of sheep red blood cells (SRBC) provokes brain neurotransmitter alterations, including DA variations within mesocorticolimbic regions, coinciding with or slightly preceding the peak immune response. Inasmuch as stressors disrupt responding for brain stimulation from the nucleus accumbens, possibly reflecting the anhedonic consequences of stressors, the present investigation assessed whether antigenic challenge would also influence responding for brain stimulation. Sheep red blood cell administration was found to reduce responding for brain stimulation from the nucleus accumbens, without affecting performance from the substantia nigra. The alterations of self-stimulation from the nucleus accumbens occurred at times that approximated the peak immune response. These data suggest that antigenic challenge may induce anhedonic-like effects that may be secondary to central neurochemical alterations engendered by the treatment. The possibility is also entertained that antigenic challenge may be interpreted as a stressor and contribute to alterations of affect. © 1997 Elsevier Science Inc.

Sheep red blood cells Nucleus accumbens Substantia nigra Brain stimulation Mouse

THERE is considerable evidence suggesting that alterations of central nervous system (CNS) activity may influence immune functioning (16), and conversely, that immunological manipulations affect endocrine and central neurotransmitter activity (3,11). For instance, administration of an antigen, such as sheep red blood cells (SRBC), altered hypothalamic unit activity (5,29) and influenced the levels and turnover of hypothalamic norepinephrine (NE) and serotonin (5-HT) at a time that coincided with the peak immune response (4,9,38). Paralleling the effects of immunological challenge, systemic administration of the monokine, interleukin-1 (IL-1), increased utilization and reduced the levels of hypothalamic NE (12,18, 37), and augmented tryptophan concentrations in the prefrontal cortex, hypothalamus, and brain stem (12,13). Likewise, it was demonstrated that 24 h following systemic treatment with either IL-1α or an endotoxin (lipopolysaccharide), turnover of hypothalamic NE, dopamine (DA), and 5-HT was increased (26). Although it was suggested that thermoregulatory alterations may have contributed to the central neurochemical effects of IL-1, the amine alterations reported by other laboratories (12,18) were evident following administration of subpyrogenic doses of IL-1.

In addition to hypothalamic alterations, immune activation may also affect DA turnover in the medial prefrontal cortex and the nucleus accumbens. As in the case of NE, altered DA turnover and concentrations corresponded with the time course of the immune response, although the DA changes were detected somewhat earlier in the nucleus accumbens. In contrast to the mesocorticolimbic DA variations, there was no evidence of alterations of DA activity or levels in the caudate, a prominent innervation site of the nigrostriatal pathway (38). Subsequent determination of extracellular DA availability employing microdialysis in the nucleus accumbens among freely moving rats revealed an initial DA efflux within 48 h of SRBC administration, followed by a decline of DA release at either 72 or 96 h following SRBC inoculation (39).

The profile of neurochemical alterations elicited by immunologic challenge was reminiscent of that provoked by stressors (15,19,38). In particular, stressors influence tryptophan

Requests for reprints should be addressed to Robert M. Zacharko, Carleton University, Institute of Neuroscience, Life Sciences Research Building, Ottawa, Ontario K1S 5B6, Canada.

concentrations, as well as the turnover and levels of NE in several brain regions (2,15). Moreover, aversive stimuli provoke marked DA alterations in mesocorticolimbic structures, while exerting limited effects on DA turnover in nigrostriatal regions (10,33). In effect, not only might the immune system act as a sensory organ informing the CNS of immunologic challenge (6,7,25), but the brain may interpret such challenge as a stressor (1,15). Although the hypothalamus appears to be a fundamental component of brain–immune interactions, mesolimbic DA activity is also influenced by immunologic challenge.

Although the behavioral consequences of stressors have been examined extensively, there are relatively few data describing the impact of immune system activation on behavioral or psychological processes. In rats, IL-1α treatment reduced food consumption and locomotor activity (27). Likewise, IL-1β provoked anorexia (8,19,24,28), disrupted responding for food reward (8), and altered swim performance in a "behavioral despair" paradigm (17). Consistent with these observations, intraventricular administration of an IL-1β receptor antagonist prior to inescapable foot shock eliminated the disruptive effects of the stressor in rats (23). In particular, elevated escape latencies ordinarily enhanced by uncontrollable foot shock were reduced in stressed animals and the incidence of freezing behavior associated with foot shock was also eliminated. Finally, in mice, intraventricular or intraperitoneal administration of murine IL-1α or hIL-1β (14,30) disrupted exploration of a novel environment (multicompartment chamber), without altering locomotor activity. Inasmuch as a similar effect was produced by restraint and by intraventricular corticotropin releasing factor (CRF), central IL-1 activation may act in a fashion comparable to that of a stressor. Furthermore, because the effects of IL-1 could be prevented by naloxone and the DA antagonist, sulpiride, but not by pretreatment with a CRF antagonist, the effects of IL-1 may be mediated by opioid and/or DA systems (30). Interestingly, it was recently reported that systemic administration of lipopolysaccharide, a potent immunological activator, reduced saccharin preference in rats, while chronic imipramine administration restored saccharin drinking among rats exposed to the endotoxin (32). Taken together, these data suggest that (a) immunological activation provokes behavioral alterations among infrahuman subjects that are in some instances reminscent of those induced by stressors; (b) behavioral alterations detected in animals following immune system challenge may parallel some of the symptoms of human depression; and (c) behavioral impairments induced by immune system activation in animals are responsive to pharmacological manipulations including those employed in the treatment of human depression.

It has been argued that a relationship exists between clinical depression and immune alterations (2). Although the data supporting this position are almost invariably correlational in nature, it is often assumed that immunological alterations are secondary to the affective disorder or that common mechanisms subserve both. Yet, immunological changes, by virtue of the effects on central neurotransmitter activity, might contribute to the emergence of depressive symptoms. We sought to determine whether antigenic challenge in animals could elicit behavioral symptoms comparable to those engendered in an animal model of depression. Of the various symptoms of depression, one of the most common is that of anhedonia. In assessing anhedonia in an animal model we examined, among other things, responding for intracranial self-stimulation from different brain regions following exposure to uncontrollable stressors. Typically, when electrodes are implanted in either mesocorticolimbic (e.g., ventral tegmentum, nucleus accumbens, medial prefrontal cortex) or nigrostriatal regions (e.g., substantia nigra, caudate), animals will perform an operant to receive electrical brain stimulation. Following exposure to an uncontrollable stressor, responding for brain stimulation from the former regions declines appreciably, whereas performance from the latter regions is hardly affected (33). The region-specific effects of stressors on brain stimulation suggest that altered self-stimulation performance cannot be attributed to the influence of variations in locomotor activity, attention, or other similar nonspecific factors. In view of the observation that disruption of responding for brain stimulation can be antagonized by enkephalin administration, it is likely that neuropeptide variations also contribute to the stressor provoked behavioral change (21). Likewise, the finding that repeated treatment with the tricyclic antidepressant, desmethylimipramine, antagonized the disruption of responding from the nucleus accumbens and the medial prefrontal cortex lends credence to the proposition that this behavior may be suitable as an animal model of depression (31,34). The present investigation attempted to determine whether (a) immunologic challenge, like stressor exposure, would influence responding for electrical brain stimulation, (b) such effects, like those provoked by stressors, were apparent when electrodes were positioned in the nucleus accumbens but not in the substantia nigra, and (c) the alterations of responding for electrical stimulation from the nucleus accumbens corresponded with the course of immune alterations engendered by SRBC treatment.

METHOD

Subjects

A total of 22 naive, male, CD-1 mice, obtained from Charles River Laboratories, St. Constant, Quebec, at approximately 6 weeks of age were acclimatized to the laboratory for approximately 6 weeks before serving as experimental subjects. During this period mice were housed in groups of 5, maintained on a 12-h light–dark cycle and permitted free access to food and water.

Surgery

Following acclimitization to the laboratory, mice were anesthetized with sodium pentobarbital (Somnotol, 65 mg/kg) and stereotaxically implanted with a bipolar stimulating electrode in either the nucleus accumbens ($n = 12$) or the substantia nigra ($n = 10$). Stereotaxic coordinates were determined from available mouse brain atlases and previous histological investigations in the CD-1 mouse in this laboratory (36). Nucleus accumbens: AP +1.0 mm from Bregma, L +0.8 to +1.0 mm from the midline, and V −4.0 to −4.2 mm from a flat skull surface. Substantia nigra: AP −3.0 mm from Bregma, L +1.2 mm from the saggital suture, and V −4.9 to −5.1 mm from skull surface. All animals were maintained on warm heating pads for 3 days postoperatively and supplemented with a wet mash diet (Sustagen) prior to being returned to the main animal housing unit. All mice were permitted a ten day postoperative recovery period before the initiation of behavioral testing.

Procedure

Mice were trained to respond for brain stimulation until stable performance was achieved. Brain stimulation for the nucleus accumbens varied between 15 and 25 μA (base to peak) at a constant stimulation frequency of 80 Hz. Mice responding for brain stimulation from the substantia nigra were

trained at current intensities between 20 and 30 μA and stimulation frequencies between 80 and 90 Hz. Pulse width (0.3 ms) and pulse duration (0.1 s) remained constant for all animals tested from the nucleus accumbens and the substantia nigra. The range of stimulation parameters employed was adjusted for each animal to elicit reliable response rates. Self-stimulation tests were 15 min in duration for the substantia nigra and 30 min for the nucleus accumbens. All animals were trained to respond for brain stimulation in 30 (diameter) × 24 cm high white polyethylene tubs. The floor of each tub contained a 2-cm well positioned in the center of the chamber. Head dipping through a distance of 1 cm interrupted a photobeam, resulting in the delivery of monophasic square wave stimulation by a constant current stimulator (Schnabel Electronics).

Once stable rates of responding were established (<10% change in response rate on 4 consecutive days) half the mice received an intraperitoneal injection of SRBC (10^6 cells), while the remaining mice received an equivalent volume of saline. In the CD-1 mouse, the peak immune response occurs 4 days following SRBC inoculation, and this dosage of SRBC was previously shown to influence DA activity within the nucleus accumbens (38,39). One hour following either SRBC or saline treatment and at 24-h intervals over the ensuing 6 days, mice were individually tested for self-stimulation from either the nucleus accumbens (Experiment 1) or substantia nigra (Experiment 2).

At the conclusion of behavioral testing, all mice were lightly anesthetized and blood samples were taken by cardiac puncture for analysis of serum antibody titers. Mice were subsequently perfused intracardially with physiological saline and a 10% formalin solution. The brains were excised from the cranial cavity and stored in formalin for approximately 2 weeks. These brains were subsequently blocked and frozen on a microtome. Coronal sections (40 μ) were mounted and stained with cresyl violet for histological verification.

RESULTS AND DISCUSSION

The distribution of electrode placements in the anterior mesolimbic system was confined to the medial borders of the nucleus accumbens (see Fig. 1). Electrode placements in the substantia nigra were observed to be situated in the pars compacta (see Fig. 2).

The percent of baseline responding for electrical brain stimulation from the nucleus accumbens of mice that received SRBC or saline is shown in Fig. 3 (upper panel). Analysis of variance of the percentage scores revealed that the SRBC treatment reduced responding for brain stimulation, $F(1, 10) = 14.86$, $p < 0.01$. It was expected that such an outcome would vary over days following inoculation, being particularly marked at the time of the peak immune response (i.e., on day 4), and to a lesser extent on day 3 following immunization. The analysis of variance, however, revealed that responding for brain stimulation following SRBC inoculation did not in-

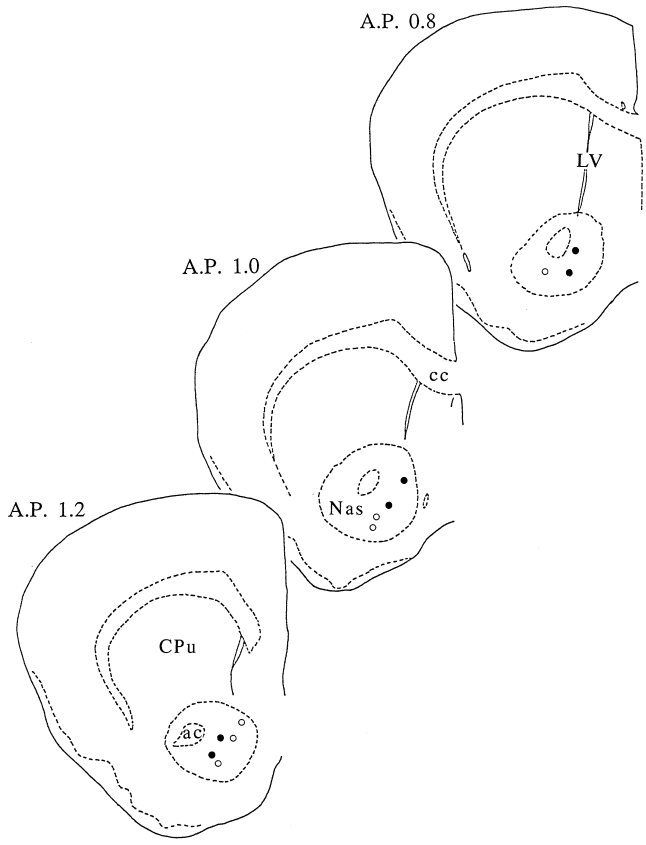

FIG. 1. Schematic representation of electrode placements in the nucleus accumbens of CD-1 mice responding for electrical brain stimulation. Closed circles denote mice treated with SRBC; open circles denote mice treated with saline.

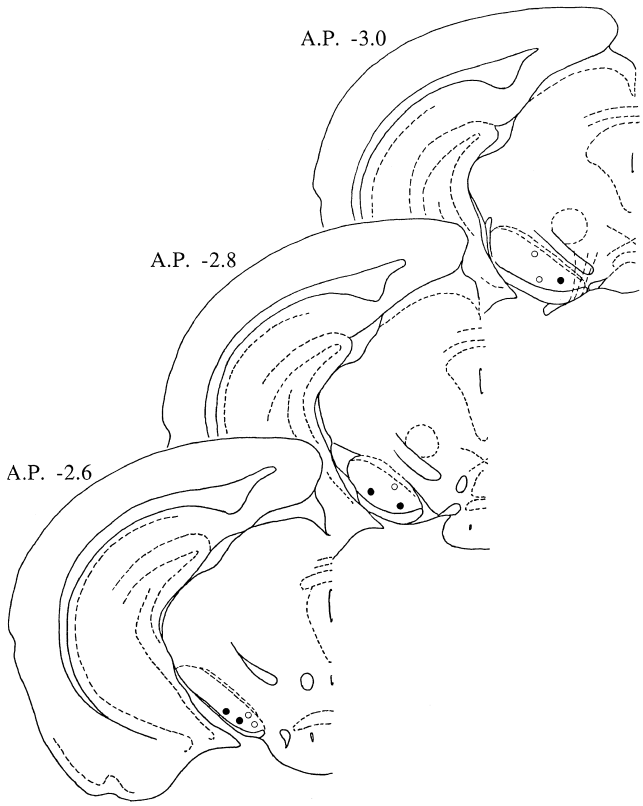

FIG. 2. Schematic representation of electrode placements in the substantia nigra pars compacta of CD-1 mice responding for electrical brain stimulation. Closed circles denote mice treated with SRBC; open circles denote mice treated with saline.

teract with days. It is noteworthy, as seen in Fig. 3 (top panel), that among saline-treated animals performance was relatively stable over days, and within-day variability was relatively small. In contrast, in SRBC-treated mice the variability was quite pronounced, particularly on days 3, 4, and 5. In fact, inspection of the performance of individual animals (see Fig. 4) indicated that two mice displayed reductions of performance on day 3 following inoculation, two animals displayed reductions on day 4, and two mice displayed response reductions that were maximal on day 5. Inasmuch as the peak immune response in CD-1 mice occurs on day 4 and does not vary appreciably across mice in this respect, such pronounced variability might not have been expected with respect to the alterations of responding for brain stimulation. However, as indicated earlier, we observed that DA changes in postmortem tissue following SRBC administration revealed that amine variations were evident both 3 and 4 days following SRBC inoculation (38). Moreover, in studies where extracellular DA was determined in freely moving rats, we observed that DA changes associated with SRBC inoculation occurred on day 3 in some animals and day 4 in others (39). The source for the intersubject differences in our rats studies, as in the present investigation, is not known; however, it is interesting that the between-days variability is not unique to the present investigation.

In contrast to the alterations of self-stimulation from the nucleus accumbens, SRBC treatment did not affect performance of mice with electrodes implanted in the substantia ni-

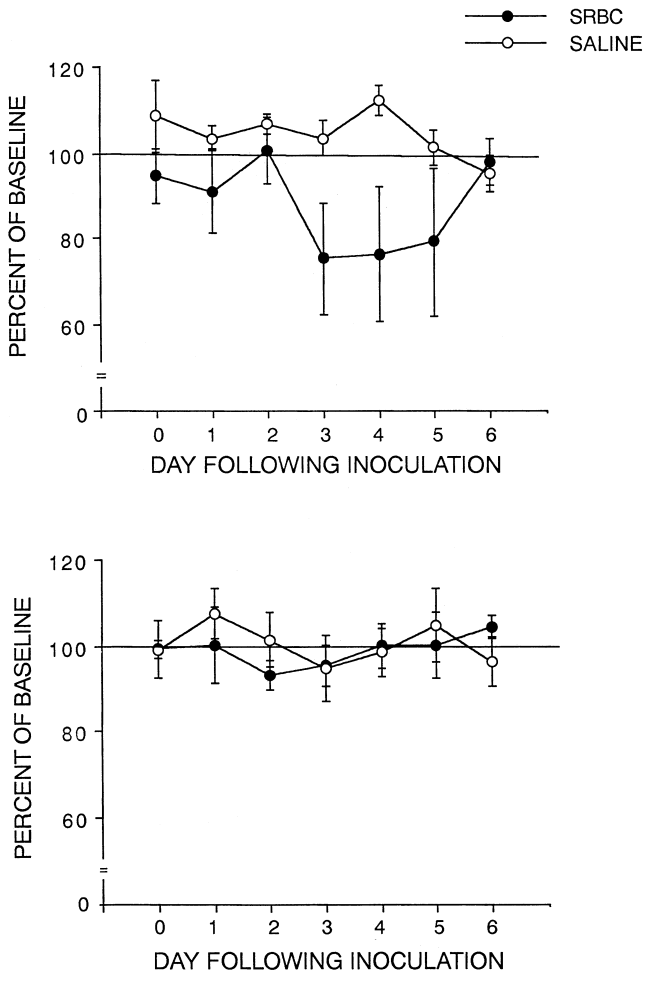

FIG. 3. Percentage of baseline self-stimulation performance (± SEM) from the nucleus accumbens (top panel) or substantia nigra (bottom panel) of mice that received either SRBC or saline treatment. Mice were tested for brain stimulation commencing 1 hour after intraperitoneal inoculation with SRBC and at 24-h intervals thereafter.

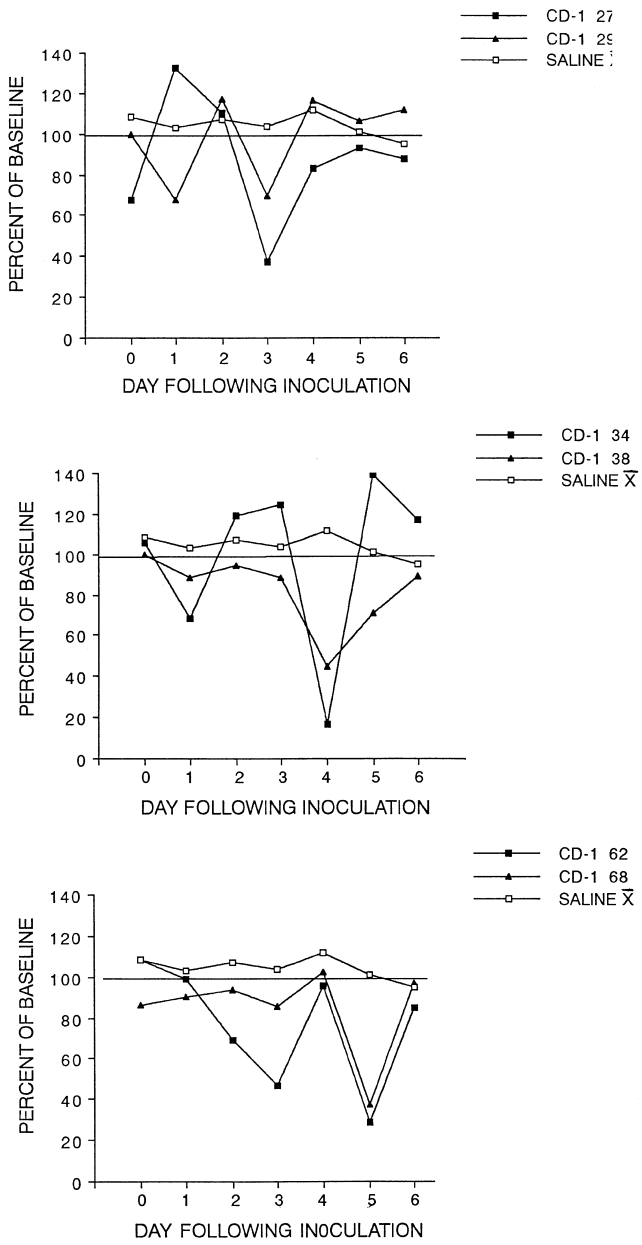

FIG. 4. Percentage of baseline self-stimulation performance from the nucleus accumbens in each of six mice that received SRBC inoculation. Note: the intersubject variability over days following SRBC administration (see text for details). The open squares represent the mean change in responding for brain stimulation of saline-treated mice.

gra ($F < 1$). As seen in Fig. 3 (bottom panel), performance was stable and relatively nonvariable across test sessions. In view of this region-specific effect of SRBC on self-stimulation, it cannot be argued that the effects of the antigenic challenge on responding for brain stimulation from the nucleus accumbens stemmed from nonspecific effects, such as general malaise or variations of locomotor activity or exploration. Afterall, if such factors contributed to the altered self-stimulation performance, then such variations should have appeared regardless of whether electrodes were implanted in the substantia nigra or the nucleus accumbens. These data support the contention that behavioral correlates of central responsivity to immune system activation can be identified in some paradigms and that detection of such alterations may be brain region specific.

Paralleling the region specific DA changes elicited by stressors (10,20,33), it was demonstrated previously that exposure to foot shock reliably disrupted responding for self-stimulation from the nucleus accumbens, but had no effect on responding for brain stimulation from the substantia nigra (35). Accordingly, it was suggested that the effects of the stressor on responding for electrical brain stimulation may have been occasioned by the region-specific influence of the aversive stimulation on central DA activity, although a role for other neurotransmitters (e.g., enkephalins) is also likely (33). It was similarly reported that SRBC administration, like uncontrollable foot shock, affected the turnover of DA within the nucleus accumbens (38). Accordingly, the possibility ought to be considered that the altered self-stimulation profile observed in the present investigation may reflect the anhedonic consequences of SRBC challenge, which is interepreted as a stressor. As indicated earlier, numerous reports have shown that depression is often associated with reduced immune functioning. Although these data are correlational, it is often assumed that depression, like stressful events, is responsible for altered immune activity. The results of the present investigation are commensurate with the view that immunological challenge may come to elicit behaviors reflective of depression, and hence, the possibility should be entertained that immunological alterations may contribute to variations of affective state. Interestingly, noradrenergic responsivity to immunological activation and vegetative symptoms of depression have been linked to neuronal alterations in the locus coeruleus, the hippocampus and the hypothalamus (22). The data of the present investigation suggest that motivational state as assessed by intracranial self-stimulation provides a direct index of mesolimbic responsivity to immunlogic challenge, and consequently, a prominent symptom of depression, anhedonia.

ACKNOWLEDGEMENTS

This work was supported by grants A1087 and A9845 from the Natural Sciences and Engineering Research Council of Canada and by a grant generously provided by the Gustavus and Louis Pfeiffer Research Foundation.

REFERENCES

1. Anisman, H.; Zalcman, S.; Zacharko, R. M.: The impact of stressors on immune and central neurotransmitter activity: Bidirectional communication. Rev. Neurosci. 4:1–34; 1993.
2. Anisman, H.; Zalcman, S.; Shanks, N.; Zacharko, R. M.: Multisystem regulation of performance deficits induced by stressors: An animal model of depression. In: Boulton, A.; Baker, G.; Martin-Iverson, M., eds. Neuromethods: Animal models of psychiatry. Clifton, NJ: Humana Press; 1991:1–59.
3. Besedovsky, H. O.; Del Rey, A.: Physiological implications of the immune-neuro-endocrine network. In: Ader, R.; Felten, D. L.; Cohen, N., eds. Psychoneuroimmunology. San Diego: Academic Press; 1991:589–608.
4. Besedovsky, H.; Del Rey, A.; Sorkin, E.; Da Prada, M.; Burri, R.; Honegger, C.: The immune response evokes changes in noradrenergic neurons. Science 221:564–566; 1983.
5. Besedovsky, H. O.; Sorkin, E.; Felix, D.; Haas, H.: Hypothalamic changes during the immune response. Eur. J. Immunol. 7:323–325; 1977.
6. Blalock, J. E.: Production of peptide hormones and neurotransmitters by the immune system. In: Ishizaka, K.; Lachmann, P. J., eds. Chemical immunology. Basel: Karger; 1992:1–24.
7. Blalock, J. E.: The immune system as a sensory organ. J. Immunol. 132:1067–1070; 1984.
8. Bluthe, R. M.; Dantzer, R.; Kelley, K. W.: CRF is not involved in the behavioural efffects of peripherally injected interleukin-1 in the rat. Neurosci. Res. Commun. 5:149–154; 1989.
9. Carlson, S. L.; Felten, D. L.; Livnat, S.; Felten, S. Y.: Alterations of monoamines in specific central autonomic nuclei following immunization in mice. Brain Behav. Immunity 1:52–63; 1987.
10. Deutch, A. Y.; Roth, R. H.: The determinants of stress-induced activation of the prefrontal cortical dopamine system. In: Uylings, H. B. M.; Van Eden, C. G.; De Bruin, J. P. C.; Corner, M. A.; Feenstra, M. G. F., eds. Progress in brain research. New York: Elsevier; 1990:367–403.
11. Dunn, A. J.: Interleukin-1 as a stimulator of hormone secretion. Prog. Neuro. Endocrinol. Immunol. 3:26–34; 1990.
12. Dunn, A. J.: Changes in plasma and brain tryptophan and brain serotonin and 5-hydroxyindoleacetic acid after foot shock stress. Life Sci. 42:1847–1853; 1988.
13. Dunn, A. J.; Welch, J.: Stress- and endotoxin-induced increases in brain tryptophan and serotonin metabolism depend on sympathetic nervous system activity. J. Neurochem. 57:1615–1622; 1991.
14. Dunn, A. J.; Antoon, M.; Chapman, Y.: Reduction of exploratory behavior by intraperitoneal injection of interleukin-1 involves brain corticotropin-releasing factor. Brain. Res. Bull. 26:539–542; 1991.
15. Dunn, A. J.; Powell, M. L.; Meitin, C.; Small, P. A.: Virus infection as a stressor: Influenza virus elevates plasma concentrations of corticosterone, and brain concentrations of MHPG and tryptophan. Physiol. Behav. 45:591–594; 1989.
16. Felten, D. L.; Cohen, N.; Ader, R.; Felten, S. Y.; Carlson, S. L.; Roszman, T. L.: Central neural circuits involved in neural-immune interactions. In: Ader, R.; Felten, D. L.; Cohen, N., eds. Psychoneuroimmunology. San Diego: Academic Press; 1991:3–25.
17. Hellerstein, M. K.; Meydani, S. I.; Meydani, M.; Wu, K.; Dinarello, C. A.: Interleukin-1-induced anorexia in the rat. Influence of prostaglandins. J. Clin. Invest. 84:228–235; 1989.
18. Kabiersch, A.; Del Rey, A.; Honegger, C. G.; Besedovsky, H. O.: Interleukin-1 induces changes in norepinephrine metabolism in the rat brain. Brain Behav. Immun. 2:267–274; 1988.
19. Kent, S.; Bluthe, R. M.; Kelley, K. W.; Dantzer, R.: Sickness behavior as a new target for drug development. Trends Pharmacol. Sci. 13:24–28; 1992.
20. LeMoal, M.; Simon, H.: Mesocorticolimbic dopaminergic network: Functional and regulatory roles. Physiol. Rev. 71:155–234; 1991.
21. Maddeaux, C.; Zacharko, R. M.: Intraventricular administration of D-Ala^2-Met^5-enkephalinamide induces rapid recovery of responding for electrical brain stimulation from the ventral tegmental area following uncontrollable footshock. Brain Res. Bull. 28:337–341; 1991.
22. Maes, M.; Smith, R.; Scharpe, S.: The monocyte-T-lymphocyte hypothesis of major depression. Psychoneuroendocrinology 20: 111–116; 1995.

23. Maier, S. F.; Watkins, L. R.: Intracerebroventricular interleukin-1 receptor anatgonist blocks the enhancement of fear conditioning and interference with escape produced by inescapable shock. Brain Res. 695:279–282; 1995.
24. McCarthy, D. O.; Kluger, M. J.; Vander, A. J.: The role of interleukin-1 in the suppression of food intake during infection. Am. J. Clin. Nutr. 42:1179–1182; 1985.
25. McEwen, B.; Brinton, R.; Chao, H.; Coirini, H.; Gannon, M.; Gould, E.: The hippocampus: A site for modulatory interaction between steroid hormones, neurotransmitters and neuropeptides. In: Muller, E. R.; MacLoed, R., eds. Neuroendocrine perspectives. New York: Springer; 1990:93–131.
26. Mefford, I. N.; Heyes, M. P.: Increased biogenic amine release in mouse hypothalamus following immunological challenge: Antagonism by indomethacin. J. Neuroimmunol. 27:55–61; 1990.
27. Otterness, I. G.; Seymour, P. A.; Golden, H. W.; Reynolds, J. A.; Daumy, G. O.: The effects of continuous administration of murine interleukin-1a in the rat. Physiol. Behav. 43:797–804; 1988.
28. Plata-Salaman, C. R.: Immunomodulators and feeding regulation: A humoral link between the immune and nervous systems. Brain. Behav. Immun. 3:193–213; 1989.
29. Saphier, D.; Abramsky, O.; Mor, G.; Ovadia, H.: Multiunit electrical activity in conscious rats during an immune response. Brain Behav. Immun. 1:40–51; 1987.
30. Spadaro, F.; Dunn, A. J.: Intracerebroventricular administration of interleukin-1 to mice alters investigation of stimuli in a novel environment. Brain Behav. Immun. 4:308–322; 1990.
31. Wolfe, C.; Zacharko, R. M.: Desmethylimipramine promotes recovery of self-stimulation from the prefrontal cortex following footshock. Brain Res. Bull. 27:601–604; 1991.
32. Yirmiya, R.: Endotoxin produces a depressive-like episode in rats. Brain Res. 711:163–174; 1996.
33. Zacharko, R. M.; Anisman, H.: Stressor-induced anhedonia in the mesocorticolimbic system. Neurosci. Biobehav. Rev. 15:1–15; 1991.
34. Zacharko, R. M.; Bowers, W. J.; Kelley, M. S.; Anisman, H.: Prevention of stressor-induced disturbances of self-stimulation by desmethylimipramine. Brain Res. 321:175–179; 1984.
35. Zacharko, R. M.; Bowers, W. J.; Kokkinidis, L.; Anisman, H.: Region-specific reductions of intracranial self-stimulation after uncontrollable stress: Possible effects on reward processes. Behav. Brain Res. 9:129–141; 1983.
36. Zacharko, R. M.; Kasian, M.; Irwin, J.; Zalcman, S.; Lalonde, G.; MacNeil, G.; Anisman, H.: Behavioral characterization of intracranial self-stimulation from mesolimbic, mesocortical, nigrostriatal, hypothalamic and extra-hypothalamic sites in the noninbred CD-1 mouse strain. Behav. Brain Res. 36:251–281; 1990.
37. Zalcman, S.; Green-Johnson, J.; Murray, L.; Dyck, D.; Anisman, H.; Greenberg, A.: Hypothalamic and hippocampal amine alterations after peripheral interleukin-1, -2 or -6 administration in mice. Soc. Neurosci. Abstr. 18:1013; 1992.
38. Zalcman, S.; Shanks, N.; Anisman, H.: Time-dependent variations of central norepinephrine and dopamine following antigen administration. Brain Res. 557:69–76; 1991.
39. Zalcman, S.; Shanks, N.; Merali, Z.; Anisman, H.: Alterations of central catecholamines associated with primary and secondary immunological challenge. Soc. Neurosci. Abstr. 17:1202; 1991.