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Differential Effects of Hypophysectomy Upon Analgesia Induced by Two Glucoprivic Stressors and Morphine

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BODNAR, R.K, D.D. KELLY, A. MANSOUR AND M. GLUSMAN. *Differential effects of hypophysectomy upon analgesia induced by two glucoprivic stressors and morphine.* PHARMAC. BIOCHEM. BEHAV. 11(3)303–308, 1979.—Pain threshold elevations induced in rats following acute exposure to stressful cold-water swims and to inescapable foot shocks are significantly attenuated by hypophysectomy. The present study investigated ths effects of hypophysectomy upon the dose-dependent and time-dependent analgesia induced by morphine and by the glucoprivic agents, 2-deoxy-D-glucose (2-DG) and insulin. Two reflex pain tests, the tail-pinch and the flinch-jump were employed. In normal rats, insulin induced prolonged (180 min) analgesia at doses of 16 U/kg on the tail-pinch test and 256 U/kg on the flinch-jump test. However, the same agents induced small and brief pain threshold elevations in hypophysectomized animals. By contrast, though 2-DG increased both measures in both groups, its effects were more marked in hypophysectomized rats. Hypophysectomized rats also exhibited a potentiated analgesic effect on both tests following high doses of morphine. On the other hand, low doses of morphine transiently increased tail-pinch thresholds in normal, but not hypophysectomized subjects. These data provide further evidence of multiple pain-inhibitory mechanisms in which the pituitary plays a complex, but integral part.

Pain Analgesia Stress Hypophysectomy Morphine Insulin 2-Deoxy-D-Glucose Rats

IN ADDITION to the well-known automatic and neuroendocrine responses to acute stress, recent evidence indicates that a temporary decline in sensitivity to painful stimuli also occurs. A number of environmental events, including inescapable foot shock, cold-water swims, immobolization, rotation, food deprivation and injections of either hypertonic saline or 2-deoxy-D-glucose (2-DG) have all been identified as analgesia-inducing stressors. Their analgesic properties in turn have been verified on a wide range of operant and reflex analgesimetric measures [1, 2, 5, 7, 10, 12, 25, 31, 32]. Only initial exposure to foot shock, cold-water swims and 2-DG stress produces analgesia. Chronic long-term exposure to the same stressors over 12–14 consecutive days results in adaptation of the analgesic effects [1, 9, 11, 30, 32], in much the same way that other autonomic and neuroendocrine stress responses adapt and that repeated morphine injections result in tolerance [34,41].

The latter similarity suggests that endophins may be involved in stress-induced analgesia. Apparent support for this contention includes the observation that adrenocorticotrophic hormone(ACTH) and B-endorphin are released concomitantly by the pituitary following either foot shock stress or severe trauma [24]. These stress-related increases in B-endorphin occur in plasma, but not brain tissue [40] and can be blocked by either hypophysectomy [24] or by dexamethasone pretreatment [19]. In addition, analgesia induced by foot shock as measured by the tail-flick test correlates with both increased radioimmunoreceptive opiate binding in brain and decreased brain levels of microinjected ^{3}H-leu-enkephalin [1, 17, 32]. However, since the time course of stress-induced analgesia has been found to vary according to both the stressor and analgesemetric test employed [1, 2, 5, 7, 10, 25, 31, 32], it is not clear what importance should be attached to these correlations. Cross-tolerance has also been shown to develop between the analgesic properties of morphine and 2-DG, such that morphine-tolerant rats do not display analgesia when acutely exposed to 2-DG [42]. In turn, 2-DG-adapted rats exhibit an attenuated analgesic response when administered morphine.

However, there is also considerable evidence for non-opiate mediation in cetain types of stress-induced analgesia. First, brain levels of microinjected ^{3}H-met-enkephalin has been found to be unaltered following foot shock [18]. Second, naloxone even at doses as high as 20 mg/kg only partially attenuates analgesia induced by both foot shock and cold-water swims [1, 8, 25, 30]. Third, dorsolateral spinal cord lesions, which attenuate both opiate-induced and stimulation-induced analgesia [4,26], fail to alter foot shock

analgesia [26]. Fourth, even though cold-water swims develops full and reciprocal cross-tolerance with the stressor 2-DG [42], it fails to develop even minimal cross-tolerance with morphine [13,32].

Most autonomic and neuroendocrine stress responses are disrupted following hypophysectomy [41]. Yet, no clear consenus has been reached as to its effects upon basal pain thresholds. Both nociceptive hypersensitivity and negative effects have been reported in hypophysectomized rats [6, 20, 21, 22, 28, 37], and in fact, decreased clinical pain reports have been described in human cancer patients following hypophysectomy [28,36]. The effects of this operation upon analgesic manipulations show similar variability since it has been reported to potentiate morphine analgesia [28,37], while attenuating analgesia induced by acupuncture [38], cold-water swims [6], immobilization [3] and inescapable foot shock (Reference Note 2).

Since the analgesia induced by cold-water swims and that induced by morphine are experimentally diassociable [6, 13, 28, 31, 37], and since 2-DG analgesia interacts with both [42], the present study compared the effects of hypophysectomy upon the analgesic effectiveness of this glucoprivic stress agent [16, 27, 39, 46], a second glucoprivic stressor, insulin [15] and morphine. Two pain tests were employed; the tail-pinch test which measures reactivity to pressure, and the flinch-jump test which measures reactivity to electric shock.

EXPERIMENT 1

Hypophysectomy, analgesia and Tail-Pinch Thresholds

METHOD

Eighteen normal (Holtzman) and eighteen hypophysectomized (HYP) (Zivic-Miller) male albino Sprague-Dawley rats, matched for body weight (250–300 g), served as subjects. For one month prior to and through out the experiment, the rats were housed in single cages and were maintained on an ad lib diet of lab chow and water. The HYP animals received daily intraperitoneal corticosterone (0.2 mg/100 g body weight) and l-thyroxin (2 ug/100 g body weight) injections to maximize the probability of survival following stress exposure. The normal rats did not receive endocrine injections. Following experimental testing, pituitary status was determined for each animal by microscopic histological examination. Complete removal of the pituitary was verified in all HYP subjects with no additional observable damage to adjacent neural tissue.

All animals were tested for tail pinch pain thresholds which was defined as the lowest pressure (g/sq in) delivered to a rat's tail which elicited tail withdrawal and/or hindpaw struggling in the experimenter's grasp. For each determination pressure was applied at a linearly-increasing rate by a motor-driven analgesy meter (Ugo Basile, Milan) 8 cm proximal from the tip of the animal's tail. Single-trial threshold determinations were made immediately prior to, and then at 30, 60, and 180 min following an injection. To assay for motor deficits, a brief neurological examination [15] was also conducted following each of the four post-injection measurements. The neurological examination consisted of rating sensory-motor abilities ranging from hyper-responsiveness to sedation. Sensory responsivity to tactile stimulation of the vibrissae and paws were assessed as well as determinations of motor impairments, if any, in each rat's posture, gait, walking or grasping abilities.

The first group consisted of six normal and six HYP rats that were injected with insulin in ascending doses of 1, 8, 16, 32 and 64 U (1 ml normal saline/kg body weight, SC). Three placebo injections were also interspersed with the five insulin doses for a total of eight injection days. The second group of six normal and six HYP rats was injected with 2-DG in ascending doses of 100, 200, 400, and 600 mg (2 ml sterile water/kg body weight, IP). Three placebo injections were also interspersed with the four 2-DG doses for a total of seven injection days. The third group of six animals and six HYP rats was injected with morphine in ascending doses of 1, 2.5, 5 and 10 mg (1 ml buffered solution/kg body weight, SC) and with three interpolated placebo injections for a total of seven injection days. Ninety-six hours separated each injection. The tester was uninformed as to the drug conditions.

Alterations in tail-pinch thresholds were measured separately for each subject by subtracting its pre-injection tail-pinch threshold from each of its corresponding post-injection thresholds. The difference scores for placebo injections were pooled within each group for HYP and normal subjects separately and for each condition. Then separate, mixed, split-plot three-way analyses of variance were performed on the three groups in which the main effect of normal and HYP subjects were the independent measure, while the main effects of dose level and post-injection test times were repeated measures [29].

RESULTS

Figure 1 shows that while insulin induced clear dose-dependent and time-dependent increases in tail-pinch thresholds of normal rats, the analgesic effectiveness of insulin in HYP rats was markedly reduced in terms of magnitude, duration and effective dose. The three-way mixed, split-plot analysis of variance revealed that insulin's analgesic effects differed significantly between the HYP and normal subjects $F(1,10)=24.60$, $p<0.01$, as well as across dose levels, $F(5,50)=5.31$, $p<0.01$, and post-injection test times, $F(3,30)=4.15$, $p<0.05$. Post-hoc Scheffe' comparisons were made between the pooled placebo data and each drug dose across the series post-injection test times. Normal rats displayed significant analgesia at all insulin doses with peak analgesic duration achieved at the 16 U dose. In contrast, HYP rats failed to display significant analgesia except for a transitory increase 30 min after administration of 32 U of insulin. Thus hypphysectomy appeared to block the analgesia normally induced by insulin.

Figure 2 indicates that 2-DG, unlike insulin, induced greater analgesia in HYP rats than in normal rats. The split-plot analysis of variance revealed that 2-DG analgesia differed significantly between the HYP and normal subjects $F(1,10)=16.62$, $p<0.01$), across the repeated measure of dose, $F(4,40)=19.70$, $p<0.01$),but not across post-injection test times, $F(3,30)=0.53$. Post-hoc Scheffe' comparisons indicated that normal rats displayed significant time-dependent elevations in tail-pinch thresholds following the 400 and 600 mg doses of 2-DG. By contrast, HYP animals displayed significant analgesia over the entire post-injection time course following these doses, and for 60 min following the 200 mg dose of 2-DG. Furthermore, the HYP rats also showed significantly greater analgesia than normal subjects at the 400, $F(1,46)=23.91$, $p<0.01$, and 600, $F=11.53$, $p<0.01$) 2-DG doses.

Figure 3 shows that the analgesic effects of morphine were both dose- and time-dependent in all rats. While mor-

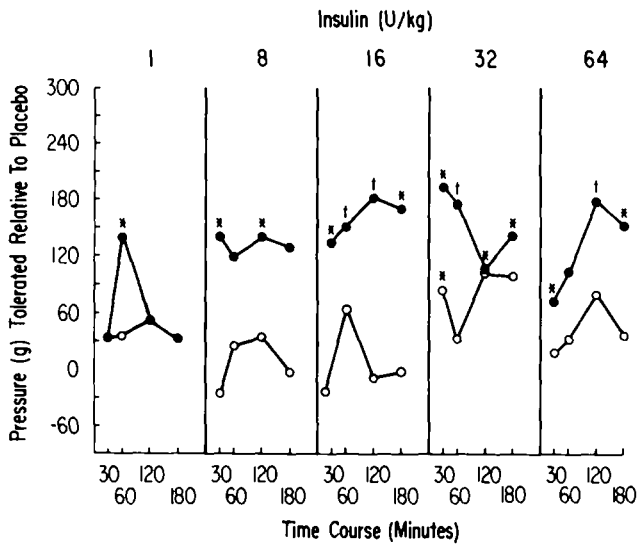

FIG. 1. Alterations in tail-pinch thresholds following insulin administration for 6 normal (solid cirlcles) and 6 hypophysectomized (open circles) rats across dose and post-injection time course. The mean difference scores were derived for each data point by the following formula: Difference Score=(Post Drug - Pre Drug) - (Post Pooled Placebo - Pre Pooled Placebo). *: $p<0.05$; + : $p<0.01$.

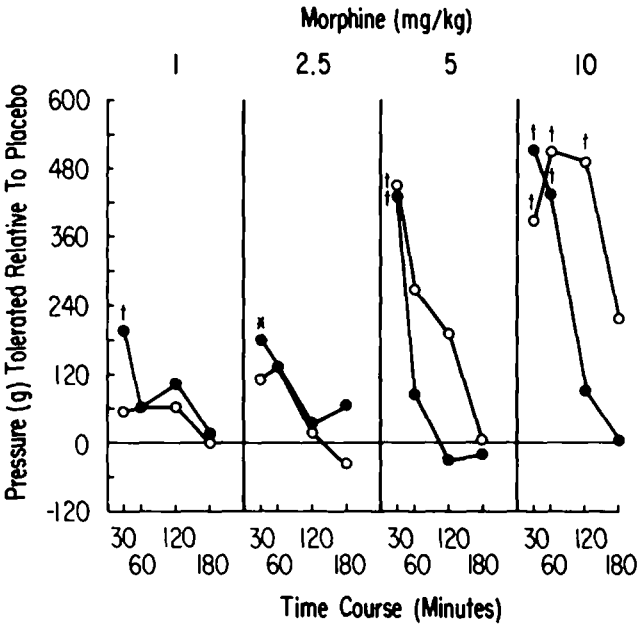

FIG. 3. Alterations in tail-pinch thresholds following morphine administration for 6 normal (solid circles) and 6 hypophysectomized (open circles) rats across dose and post-injection time course. The difference scores were computed as in Fig. 1. *:$p<0.05$; +: $p<0.01$.

phine's analgesic effectiveness differed significantly across the repeated measures of dose levels, $F(4,40)=20.48$, $p<0.01$ and post-injection test times, $F(3,30)=8.56$, $p<0.01$, its effects upon normal and HYP rats did not differ, $F(1,10)=0.11$. The latter statistical result was due in part to a systematic variation in the analgesic responsivity of the HYP rats to the

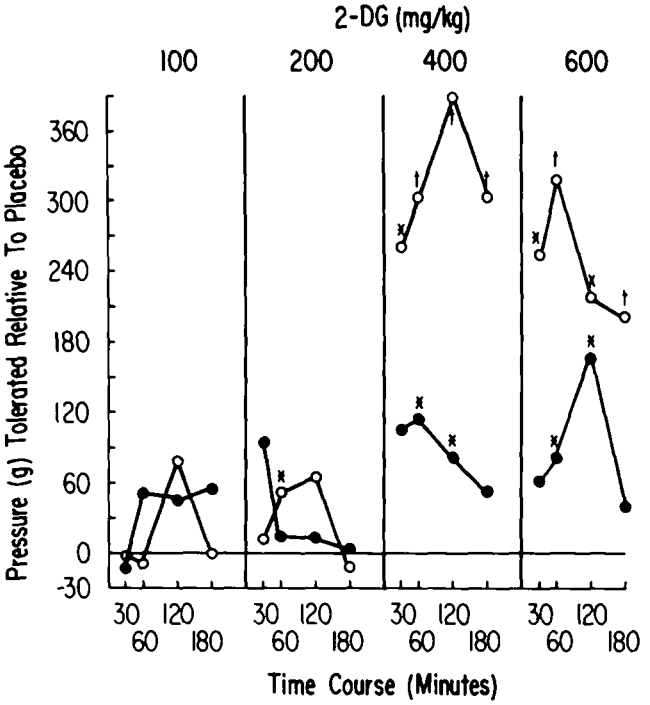

FIG. 2. Alterations in tail-pinch thresholds following 2-deoxy-D-glucose (2-DG) administration for 6 normal (solid circles) and 6 hypophysectomized (open circles) rats across dose and post-injection time course. The difference scores were computed as in Figure 1. *:$p<0.05$; +: $p<0.01$.

successively higher doses of morphine. Whereas normal rats displayed significant elevations in tail-pinch thresholds within 30 min following morphine at the two lowest doses, HYP rats did not. Subsequently both groups displayed significant analgesia following morphine at 5 and 10 mg/kg, but the HYP rats exhibited significantly longer and more pronounced analgesia, particularly at the highest dose, $F(1,46)=4.14$, $p<0.05$. Thus, successive, increasing doses of morphine had different effects in normal and HYP rats with the latter exhibiting less responsivity than normal to the initial low doses and greater responsivity to the subsequent high doses.

The neurological examination failed to reveal sensory-motor deficits in any subject or drug condition with the exception of one HYP rat which showed a mild sensory-motor deficit following 1 U of insulin and severe deficits following the 32 U insulin dose. The failure of the present study to observe the moderate neurological dysfunction following administration of insulin as described by Brandes [15] may reflect some procedural differences in the examination. However, the observation that both HYP and normal subjects appeared to behave similarly in the examination suggests that the differences in analgesic responsivity are apparently due to some changes in endogenous pain-inhibition rather than a non-specific effect.

EXPERIMENT 2

Hypophysectomy, Analgesia and Flinch-Jump Thresholds

The first experiment showed that while analgesia induced by high doses of morphine and of 2-DG was potentiated in

HYP rats, the analgesia induced by insulin was attenuated by this procedure in the same manner as that induced by cold-water swims, immobilization and inescapable foot shock [3,6] Reference Note 2. The second experiment examined whether hypophysectomy's differential effects upon the analgesic responsivity of these drugs could be replicated using another reflex pain measure, the flinch-jump test. Moreover, to determine whether the administered endocrine supplements accounted for the observed differences, the HYP subjects in the second experiment did not receive endocrine supplements.

METHOD

Six naive normal and six naive HYP rats which received no supplementary hormone injections served as subjects. All animals were tested for flinch-jump thresholds in a plexiglass chamber with a 30 cm by 24 cm floor composed of 14 bars through which scrambled electric foot shocks were delivered. Using an ascending method of limits of successively more intense shocks, the flinch threshold was defined in mA as the lowest intensity that elicited a withdrawal of a single paw from the grids. The initial jump threshold was defined as the lowest intensity which elicited simultaneous removal of both hindpaws from the grids. The jump threshold was defined as the lowest of the two consecutive intensities which elicited a jump as above. Each of six daily trials began with the animal receivinv a 300-msec foot shock at a current intensity of 0.1 mA. Subsequent shocks followed every 10 sec in 0.05 mA increments until each nociceptive threshold was determined. Daily flinch, initial jump and jump thresholds were expressed as a mean of these six trials. Four days of stable baseline thresholds were determined for each animal. Finch-jump thresholds were determined 30 min after each of the following series of injections which were randomized across subjects: saline (1 ml/kg body weight, IP), saline (1 ml/kg body weight, SC), 2-DG at doses of 400 and 600 mg/kg (300 mg 2-DG/ml normal saline /kg body weight, IP), morphine (5 mg/ml buffered solution/kg body weight, SC), and insulin at doses of 64, 128 and 256 U (100 Iletin insulin/ml normal saline/kg body weight, SC). Seventy-two hours separated each injection. The tester was uninformed as to the experimental conditions.

RESULTS

Figure 4 shows that, similar to the results of Experiment 1, hypophysectomy potentiated both 2-DG and morphine analgesia, but attenuated insulin analgesia. Separate one-way analyses of variance revealed significant differences among the experimental conditions for both normal $F(5,48)=6.18$, $p<0.01$, and HYP, $F=23.61$, $p<0.01$, subjects. Post-hoc Scheffe' comparisons indicated that normal animals exhibited significant increases in jump thresholds over placebo following only the 600 mg/kg, $F(1,10)=45.60$, $p<0.01$, dose of 2-DG. However, the unsupplemented HYP animals displayed significantly greater analgesia than placebo at both the 400 mg/kg, $F=54.83$, $p<0.01$, and 600 mg/kg, $F=44.94$, $p<0.01$, 2-DG doses and significantly greater analgesia as compared to normals at the 400 mg/kg ($F=6.91$, $p<0.05$) dose of 2-DG. Also similar to the results of Experiment 1, while the single 5 mg/kg dose of morphine produced a significant ($F=9.90$, $p<0.01$) analgesic effect in normal rats, it produced an even greater effect in the unsupplemented HYP rats. Morphine analgesia in these rats was significant relative to their own placebo values ($F=61.95$, $p<0.01$) and significantly greater than the analgesia induced in normal subjects ($F=10.97$, $p<0.01$).

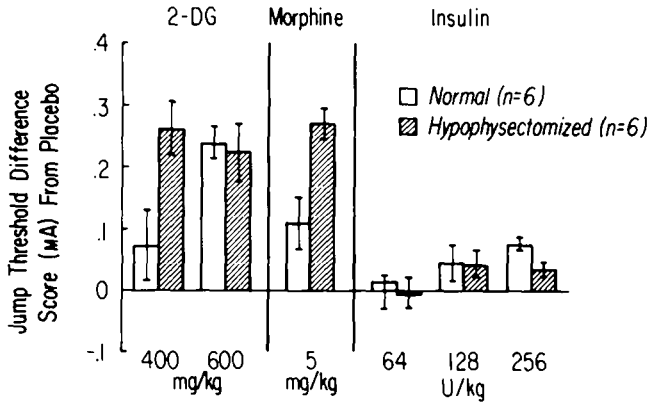

FIG. 4. Alterations in jump thresholds in normal and hypophysectomized rats following administration of either 2-deoxy-D-glucose (2-DG), morphine or insulin.

Insulin analgesia measured by the flinch-jump test differed only in sensitivity from that measured by the tail-pinch test in Experiment 1. The modest elevations in jump threshold elevations induced in the normal animals failed to reach statistical significance following both the 64 U ($F=0.12$) and the 128 U ($F=1.84$) insulin doses. An insulin dose of 256 U was necessary to induce significant ($F=5.74$, $p<0.01$) analgesia relative to placebo. Thus, flinch-jump thresholds appeared less sensitive than tail-pinch thresholds to the analgesic effects of insulin in normal rats. The results in the HYP rats, however, were the same as in Experiment 1. No does of insulin induced analgesia in the unsupplemented HYP animals and they displayed a significantly smaller elevation than normals following the 256 U dose ($F=5.73$, $p<0.01$).

DISCUSSION

The present study demonstrates four noteworthy results. First, acute injections of insulin, like many stressors, induced a dose-dependent and time-dependent analgesia in normal animals with the tail-pinch test being more sensitive to insulin's analgesic effects at low doses than the flinch-jump test. Second, insulin analgesia, like that induced by cold-water swims, immobilization and inescapable foot shock ([3,6], Reference Note 2), was markedly attenuated in HYP rats regardless of the pain reflex test used. Third, the analgesia induced by 2-DG was potentiated by hypophysectomy. Fourth, in Experiment 1, successive injections of progressively higher doses of morphine produced different results in normal and HYP rats. HYP rats showed less analgesia on the tail-pinch test than normal following the initial low-dose injections and greater analgesia following the subsequent high-dose injections. The latter may be due either to a slower acquisition of opiate tolerance by HYP rats or a real potentiation of high-dose opiate analgesia in HYP rats. There is some support for the latter interpretation. First, in Experiment 2, a single, acute dose of morphine at 5 mg/kg produced greater analgesia in unsupplmented HYP rats than normals. Second, other studies [28,37] that reported a potentiated analgesic response to morphine in HYP animals employed a separate-groups design. These results

might imply that chronic absence of pituitary endorphins in HYP animals may sensitize central opiate receptors so that exposure to morphine produces an enhanced response. Moreover, the presence or absence of supplementary injections of both corticosterone and thyroxin in the HYP animals appears not to be critical for morphine's potentiated analgesic effect.

It also appears that the analgesia induced by 2-DG may similarly be mediated in part by activation of central opiate-like pain-inhibition. Morphine-tolerant rats fail to display 2-DG analgesia and 2-DG-adapted rats exhibit attenuated morphine analgesia [42]. Sub-analgesic doses of morphine interact with sub-analgesic doses of 2-DG to increase pain thresholds (Reference Note 1). However it is unlikely that 2-DG's analgesic properties are related solely to CNS endorphin activity since 2-DG analgesia is not reversed by the opiate antagonist naloxone and since 2-DG and cold-water swim analgesia exhibit complete and reciprocal cross-tolerance (Reference Note 1, [42]). As noted previously, cold-water swim and morphine analgesia fail to develop cross-tolerance [13,31].

The present study also indicates that insulin analgesia is, like cold-water swim analgesia, also dependent upon an intact pituitary for full analgesic expression. That 2-DG and insulin exert opposing nociceptive effects in hypophysectomized rats suggests that their respective generalized glucoprivic effects per se are not primarily responsible for their anti-nociceptive actions. This dissociation between the glucoprivic agents is not limited to pain reactivity. Although the hyperphagic effects of both 2-DG and insulin can be attenuated by medial forebrain bundle lesions, zona incerta lesions and adrenalectomy eliminate only 2-DG hyperphagia, while vagotomy eliminates only insulin hyperphagia [14, 23, 33, 43, 44, 45]. Thus the present data indicate that multiple mechanisms exist for the activation of intrinsic pain-inhibition and suggest that pituitary factors are influential in mediating only certain of these.

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REFERENCES

1. Akil, H., J. Madden, R. L. Patrick and J. D. Barchas. Stress-induced increase in endogenous opiate peptides: concurrent analgesia and its partial reversal by naloxone. In: *Opiates and Endogenous Opioid Peptides*, edited by H. W. Kosterlitz, Amsterdam: North Holland Pub., 1976, pp. 63-70.
2. Amir, S. and Z. Amit. Endogenous opioid ligands may mediate stress-induced changes in the effective properties of pain-related behavior in rats. *Life Sci.* **23:** 1143–1152, 1978.
3. Amir, S. and Z. Amit. The pituitary gland mediates acute and chronic pain responsiveness in stressed and non-stressed rats. *Life Sci.* **24:** 439–448, 1979.
4. Basbaum, A. I., N. J. Marley, J. O'Keefe and C. H. Clanton. Reversal of morphine and stimulus-produced analgesia by subtotal spinal cord lesions. *Pain* **3:** 45–56, 1977.
5. Bodnar, R. J., M. Glusman, A. Mansour and D. D. Kelly. Differential aterations following hypophysectomy in analgesia induced by morphine and different stressors. *Soc. Neurosci. Abstr.* **4:** 457, 1978.
6. Bodnar, R. J., M. Glusman, M. Brutus, A. Spiaggia and D. D. Kelly. Analgesia induced by cold-water stress: attenuation following hypophysectomy. *Physiol. Behav.* **23:** 53–62, 1979.
7. Bodnar, R. J., D. D. Kelly and M. Glusman. Stress-induced analgesia: time course of pain reflex alterations following cold-water swims. *Bull. Psychon. Soc.* **11:** 333-336, 1978.
8. Bodnar, R. J., D. D. Kelly, A. Spiaggia, C. Ehrenberg and M. Glusman. Dose-dependent reductions by naloxone of analgesia induced by cold water stress. *Pharmac. Biochem. Behav.* **8:** 667–672, 1978.
9. Bodnar, R. J., D. D. Kelly, A. Spiaggia and M. Glusman. Stress-induced analgesia: adaptation following chronic cold-water swims. *Bull. Psychon. Soc.* **11:** 337-340, 1978.
10. Bodnar, R. J., D. D. Kelly, A. Spiaggia and M. Glusman. Biphasic alaterations of nociceptive thresholds induced by food deprivation. *Physiol. Psychol.* **6:** 391-395, 1978.
11. Bodnar, R. J., D. D. Kelly, M. Brutus and M. Glusman. Chronic 2-deoxy-D-glucose treatment: adaptation of its analgesic, but not hyperphagic properties. *Pharmac. Biochem. Behav.* **9:** 763-768, 1978.
12. Bodnar, J., D. D. Kelly, M. Brutus, A. Mansour and M. Glusman. 2-deoxy-D-glucose-induced decrements in operant and reflex pain thresholds. *Pharmac. Biochem. Behav.* **9:** 543-549, 1978.
13. Bodnar, R. J., D. D. Kelly, S. S. Steiner and M. Glusman. Stress-produced analgesia and morphine-produced analgesia: lack of cross-tolerance. *Pharmac. Biochem. Behav.* **8:** 661-666, 1978.
14. Booth, D. A. Modulation of the feeding response to peripheral insulin, 2-deoxy-D-glucose or 3-0-methoxyglucose injection. *Physiol. Behav.* **8:** 1069-1076, 1972.
15. Brandes, J. S. Insulin induced overeating in the rat. *Physiol. Behav.* **18:** 1095-1102, 1977.
16. Brown, J. Effects of 2-deoxyglucose on carbohydrate metabolism: review of the literature and studies in the rat. *Metabolism* **11:** 1098-1112, 1962.
17. Chance, W. T., A. C. White, G. M. Krynock and J. A. Rosecrans. Conditional fear-induced antinociception and decreased binding of (^{3}H)N-leu-enkephalin to rat brain. *Brain Res.* **141:** 371-374, 1978.
18. Fratta, W., H. Y. T. Yang, J. Hong and E. Costa. Stability of met-enkephalin content in brain structures of morphine-dependent or foot shock-stressed rats. *Nature* **268:** 452-453, 1977.
19. French, E. D., F. E. Bloom, C. Rivier, R. Guillemin and J. Rossier. Morphine or stress induced increases of plasma B-endorphin and prolactin are prevented by dexamethasone pretreatment. *Soc. Neurosci. Abstr.* **4:** 408, 1978.
20. Gibbs, J., J. A. Sechzer, G. P. Smith, R. Conners and J. Weiss. Behavioral responsiveness of adrenalectomized, hypophysectomized, and intact rats to electric shock. *J. comp. physiol. Psychol.* **82:** 165-169, 1973.
21. Gispen, W. H., A. M. Van der Poel and T. J. B. Van Wimersma Greidanus. Pituitary adrenal influences on behavior: responses to test situations with or without electric foot shock. *Physiol. Behav.* **10:** 345-350, 1973.
22. Gispen, W. H., T. J. B. Van Wimersma Greidanus and D. De-Weid. Effects of hypophysectomy and ACTH 1-10 on responsiveness to electric shock in rats. *Physiol. Behav.* **5:** 143-146, 1970.
23. Grossman, S. P. and L. Grossman. Persisting deficits in rats recovered from transections of fibers which enter or leave the hypothalamus laterally. *J. comp. physiol. Psychol.* **85:** 515-527, 1973.

24. Guillemin, R., T. Vargo, J. Rossier, S. Minick, N. Ling, C. Rivier, W. Vale and F. Bloom. B-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* **197:** 1367-1369, 1977.
25. Hayes, R. L., G. J. Bennett, P. G. Newlon and D. J. Mayer. Behavioral and physiological studies of non-narcotic analgesia in the rat elicited by certain environmental stimuli. *Brain Res.* **155:** 69-90, 1978.
26. Hayes, R. L., D. D. Price, G. J. Bennett, G. L. Wilcox and D. J. Mayer. Differential effects of spinal cord lesions on narcotic and non-narcotic suppression of nociceptive reflexes: further evidence for the physiological multiplicity of pain modulation. *Brain Res.* **155:** 91-101, 1978.
27. Himsworth, R. L. Hypothalamic control of adrenaline secretion in response to insufficient glucose. *J. Physiol., Lond.* **198:** 451-455, 1970.
28. Holaday, J. W., P. Y. Law, L. F. Tseng, H. H. Loh and C. H. Li. B-endorphin: pituitary and adrenal glands modulate its action. *Proc. natn. Acad. Sci. U.S.A.* **74:** 4628-4632, 1978.
29. Kirk, R. E. *Experimental design: Procedures for the behavoral sciences.* Brooks/Cole: Belmont, Calif., 1968.
30. Lal, H., Head, T. Spaulding and S. Fielding. Swim-stress induced analgesia: study of tolerence and cross-tolerance to morphine. *Int. Congress Pharmac. Abstr.* **7:** 451, 1978.
31. Lal, H., T. Spaulding and S. Fielding. Swim-stress induced analgesia and lack of naloxone antagonism. *Communs. Psychopharmac.* **2:** 263-266, 1978.
32. Madden, J., H. Akil, R. L. Patrick and J. D. Barchas. Stress-induced parallel changes in central opioid levels and pain responsiveness in the rat. *Nature* **265:** 358-360, 1977.
33. Marshall, J. F., J. S. Richardson and P. Teutelbaum. Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *J. comp. physiol. Psychol.* **87:** 808-830, 1974.
34. Martin, W. R. Opioid antagonists. *Pharmac. Rev.* **19:** 463-521, 1967.
35. Misfeldt, D. S. and A. Goldstein. Hypophysectomy relieves pain not via endorphins. *New Engl. J. Med.* **297:** 1236-1237, 1977.
36. Moricca, G. Hypophysectomy for cancer pain. *Adv. Neurol.* **4:** 707-714, 1974.
37. Murray, W. J. and J. W. Miller. Potency differences of morphine-type agents by radiant heat and "cramping" analgesic assays providing evidence for a potentiating substance from the posterior pituitary gland. *J. Pharmac. exp. Ther.* **128:** 380-383, 1960.
38. Pomeranz, B., R. Cheng and P. Law. Acupuncture reduces electrophysiological and behavioral responses to noxious stimuli: pituitary is implicated. *Exp. Neurol.* **54:** 172-178, 1977.
39. Ritter, S. and R. C. Ritter. Protection against stress-induced brain norepinephrine depletion after repeated 2-deoxy-D-glucose adminstration. *Brain Res.* **127:** 179-184, 1977.
40. Rossier, J., E. D. French, C. Rivier, N. Ling, R. Guillemin and F. E. Bloom. Foot-shock induced stress increases B-endorphin levels in blood but not brain. *Nature* **270:** 618-620, 1977.
41. Selye, H. *The story of the adaptation syndrome.* Montreal: Acta, Inc., 1952.
42. Spiaggia, A., R. J. Bodnar, D. D. Kelly and M. Glusman. Opiate and non-opiate mechanisms of stress-induced analgesia: cross-tolerance between stressors. *Pharmac. Biochem. Behav.* **10:** 761-766, 1979.
43. Stricker, E. M. and M. J. Zigmond. Effects on homeostasis of intraventricular injections of 6-hydroxydopamine in rats. *J. comp. physiol Psychol.* **86:** 973-994, 1974.
44. Walsh, L. L. and S. P. Grossman. Loss of feeding to 2-deoxy-D-glucose but not insulin after zona incerta lesions in the rat. *Physiol. Behav.* **15:** 481-485, 1975.
45. Wayner, M. J., A. Cott, J. Millner and R. Tartaglione. Loss of2-deoxy-D-glucose induced eating in recovered lateral rats. *Physiol. Behav.* **7:** 881-884, 1971.
46. Wick, A. N., D. R. Drury, H. I. Nakada and J. B. Wolfe. Localization of the primary metabolic block produced by 2-deoxy-D-glucose. *J. Biol. Chem.* **224:** 963-969, 1957.

REFERENCE NOTES

1. Bodnar, R. J., D. D. Kelly and M. Glusman. 2-Deoxy-D-glucose analgesia: influences of opiate and non-opiate factors. *Pharmac. Biochem. Behav.* **11:** 297-301, 1979.
2. Pert, A. Hormonal and neuropeptidergic determinants of stress-induced analgesia In: Symposium: Analgesia Induced by Stress, Conditioning and other Environmental Manipulations. D. D. Kelly, Chairman: Fiftieth Annual Meeting of the Eastern Psychological Association. Philadelphia, PA, April, 1979.