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The Role of Endorphins in Animal Learning and Behavior[1]

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RILEY, A. L., D. A. ZELLNER AND H. J. DUNCAN. *The role of enaorphins in animal learning and behavior.* NEUROSCI. BIOBEHAV. REV. 4(1) 69–76, 1980.—The present review examined the influence of endorphins in animal learning and behavior. It was suggested that in learning paradigms involving stress, the stressor elicits the release of endorphins. Given the evidence on endorphin-mediated, stress-induced analgesia, it was further suggested that the stress-induced release of endorphins modulates the aversiveness of the stressor, and as such, affects the learning based on this stressor. A number of learning paradigms, e.g., the conditioned emotional response, preference for signaled shock, conditioned taste aversions, and learned helplessness, were presented in support of this mediation of learning by the endorphins. A possible interaction between the endorphins and adrenocorticotrophic hormone was offered as a physiological basis for this mediation.

Endorphins Analgesia Learning Conditioned emotional response Conditioned taste aversions Signaled shock ACTH

THE interest and development in the active peptides in the central nervous system have steadily increased within the past 10 years [8, 42, 111, 134]. While many of these centrally-acting peptides may have important roles in the occurrence of behavior [111], the present review focuses on a specific class of these peptides, i.e., the endorphins.

The identification of the endorphins followed the discovery of receptors in both the central and peripheral nervous system at which morphine and other opiates were agonists [112]. In many instances, these receptors paralleled the classical pathways for pain transmission, e.g., spinal cord, mesencephalic and diencephalic regions, and the nuclei responsible for affective responses to pain, e.g., amygdala, hippocampus, and hypothalamus [13, 67, 71, 107, 112, 119–122]. Such a parallel suggested that there may be an endogenous ligand that under conditions of stress is released and by interacting with the opiate receptor inhibits pain transmission [75,102] or the emotional responses to pain [5, 6, 112].

Recently, a number of endogenous compounds have been isolated which in bioassays for morphine activity mimic the effects of morphine, e.g., displacement of ^{3}H-dihydromorphine from receptors in the guinea pig ileum and mouse vas deferens [62,71]. The compounds, e.g., methionine enkephalin, leucine enkephalin, alpha endorphin, beta endorphin, and gamma endorphin, are collectively called the endorphins.

Following this in vitro identification of the endorphins and the subsequent analysis of their distribution in the nervous system [13, 67, 71], the biological relevance of these compounds was demonstrated, giving behavioral support to the suggestion that the endorphins may produce analgesia in response to stress.

That the endorphins may function in antinociception has come from three major lines of research. First, the exogenous administration of endorphins results in analgesia, e.g., elevations in thresholds for tail-flick or jump response [10, 35, 40, 47, 64–66, 77, 87, 117, 120, 121]. Second, a number of stressors produce an increase in blood or brain levels of the endorphins [2–4, 60, 61, 77, 82, 115, 116]. Third, in addition to altering levels of endorphins in the body, stressors in turn produce analgesia [2, 4, 14–25, 113].

While there is considerable evidence that the endorphins may modulate or attenuate pain, that this antinociception is mediated via the opiate receptors remains unclear. For example, naloxone hydrochloride, a specific narcotic receptor antagonist, has been reported both to block and fail to block stress-induced analgesia. The blocking of stress-induced analgesia provides evidence that opiate receptors may be mediating the analgesia [2, 4, 12, 24, 25, 34, 38, 50, 56, 58, 59, 63, 68]. Naloxone's failure to block stress-induced analgesia, however, suggests that a non-opiate pathway may be involved as well [24, 25, 30, 46, 51, 56, 86]. That both opiate and non-opiate systems may underlie antinociception is further evidenced in that while stress-induced analgesia diminishes with chronic or repeated exposures of the stressor [5, 6, 18], a phenomenon resembling tolerance to opiates, cross-tolerance among stressors is not always reported. For example, although the stress of 2-deoxy-D-glucose produces analgesia, after repeated exposures to 2-DG, analgesia is no

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longer produced. Yet when animals are then given an injection of morphine, analgesia is again produced [113]. That tolerance occurs to repeated exposures indicates that an opiate mechanism may be involved in stress-induced analgesia. On the other hand, the failure to observe cross-tolerance suggests that there in not a common mechanism, opiate or non-opiate, underlying the analgesia induced by all stressors.

Continuing evidence that there are multiple opiate receptors, each with differential sensitivity to naloxone and to the various endogenous endorphins [9, 71, 78, 84], could possibly account for the fact that naloxone doesn't always block an endorphin-mediated analgesia and that cross-tolerance is not always established between the analgesia induced by different stressors. Such a possibility must remain speculative, however, until there is evidence that different stressors activate the release of different endogenous endorphins.

In summary, there do appear to be endogenous peptides, the endorphins, which interact with receptors sensitive to opiates and which produce analgesia. Under some circumstances, this analgesia appears to be mediated via the endorphin/receptor interaction.

While most of the research on the endorphins and the conclusions regarding their analgesic properties and opiate parallels are based on their biochemical identification and their elicitation by specific behavioral and pharmacological challenges, recent focus has been on the endorphins and animal learning [75, 76, 102]. In addition to supporting the biochemical and behavioral evidence implicating endorphins in analgesia, the research on this topic has provided a basis for conclusions regarding the role endorphins may play in animal learning. The remainder of this review examines this evidence.

There are several lines of research implicating the endorphins as regulators of animal learning and conditioning. In the majority of this research, various stressors are used as the unconditioned stimulus in classical conditioning. Given the aforementioned discussion on stress-induced analgesia and the possible involvement of the endorphins in this analgesia, it is not surprising that learning tasks involving stress may elicit the release of endorphins which in turn modulate the aversiveness of the stress which controls conditioning.

Using a conditioned emotional response (CER) design, Schull [99] has demonstrated an interaction of the endorphins with aversive conditioning. In a CER procedure, animals are first trained to make an operant response for food or another reinforcer. After responding has stabilized, a stimulus, e.g., a light or tone, paired with shock is presented to the animal while it is responding for food. After a number of pairings of the stimulus with shock, animals typically suppress responding in the presence of the stimulus while maintaining responding in its absence. This selective depression in responding is evidence of a conditioned suppression or a conditioned emotional response. Schull has shown that if rats are given naloxone hydrochloride prior to the pairing of the stimulus with shock, the subsequent conditioned suppression is significantly greater. One explanation for this greater suppression is that during CER training, the shock, via the endorphins, attenuates its own aversiveness. While attenuated, the shock is still sufficiently aversive to result in conditioned suppression. Pretreatment with naloxone, however, blocks this stress-induced attenuation, resulting in greater aversiveness, and,consequently, greater conditioned suppression.

These results indicate a direct role of endorphins in the acquisition of specific stimulus associations, e.g., light-shock associations. By possibly altering the aversiveness of shock, the conditioned emotional response may be attenuated to some extent. Naloxone restores the shock to its non-attenuated aversiveness.

Recent work by Fanselow [39] and Chance [30] illustrates a less direct but equally effective influence on learning by the endorphins. This work involves conditioned analgesia or auto-analgesia [30].

Before addressing conditioned analgesia, it is important to examine some recent findings of Siegel [103–105] on compensatory classical conditioning. Siegel demonstrated that when a stimulus is paired with morphine, a classically-conditioned compensatory response is acquired, i.e., if morphine produces hyperthermia, the stimulus associated with morphine elicits a compensatory hypothermic response. After a number of conditioning trials, i.e., pairings of the stimulus with morphine, if the animal is injected with morphine in the presence of this stimulus, the animal shows no thermal changes due to the summation of the unconditioned hyperthermic and conditioned hypothermic responses elicited by the morphine and stimulus, respectively. Siegel has used such evidence to explain tolerance to morphine on the basis of classical conditioning.

This phenomenon of compensatory conditioning has been used to explain the rat's preference for signaled over unsignaled shock, an explanation involving the endorphins as well. When rats are allowed to choose between two sides of a shuttlebox, one side on which shock is delivered preceded by a signal and the other side on which shock is presented without a warning signal, the rat prefers the side on which the shock is signaled. While this finding has generated a range of interpretations [7], one recent interpretation is based on the endorphins. Fanselow [39] has suggested that the stimulus associated with shock on the signaled side elicits endorphins. This classically conditioned compensatory release of the endorphins reduces the aversiveness of the following shock which is paired with that stimulus. That animals prefer the side on which the shock is preceded by a stimulus over the side on which shock is unsignaled may reflect a preference for the side associated with the less aversive shock due to its signaled modulation. In support of this interpretation, Fanselow [39] demonstrated that if animals are treated with naloxone prior to being given a choice between signaled and unsignaled shock, the preference for signaled shock is no longer seen. This elimination of the preference for signaled shock can be explained by the blocking by naloxone of the conditioned attenuation of shock. Because neither side is now associated with a reduction in shock aversiveness, a preference is no longer maintained.

This compensatory conditioning interpretation of the preference for signaled shock is supported further by Chance's [30–33] independent demonstration of conditioned analgesia (see also [73,85]). Using tail flick as an assessment of analgesia, Chance reported that with repeated pairings of a light stimulus with footshock, the stimulus, alone, raised the threshold for tail flick, i.e., the stimulus produced analgesia. This demonstration of conditioned analgesia offers an empirical base for Fanselow's [39] speculation regarding the conditioned release of the endorphins and their role in the rat's preference for signaled shock.

The results from the CER and signaled shock procedure suggest that the endorphins may in part regulate the aversiveness of stressful events, and as such, may influence conditioning and learning. This discussion on the influence of endorphins in animal learning is based on tasks involving shock, a stressor which reliably elicits endorphins and which induces analgesia. Conclusions regarding analgesia and the endorphins based on these findings follow naturally from the use of a stimulus that subjectively is reported as painful.

A second series of studies using a number of stressors, including shock, has recently been presented that indicate that the endorphins may modulate not only the painful components of stress, i.e., produce antinociception, but also its general aversiveness. The design for such demonstrations involves the pairing of a novel taste with an injection of a toxin or some pharmacological stressor. Animals injected with a toxin or drug following consumption of a novel tasting solution will avoid consumption of that solution on a subsequent exposure [43,91]. The result of this taste-toxin pairing, therefore, is a conditioned aversion to the solution. The aversiveness of the toxin is presumably the condition necessary to establish this associative learning.

This design has been used in several ways to illustrate the influence of the endorphins in learning. For example, Stolerman, Pilcher, and D'Mello [114] injected rats with naloxone hydrochloride, as well as a number of other narcotic antagonists, following consumption of a novel saccharin solution (see also [41, 88, 89, 114]). These antagonists were very effective in conditioning taste aversions, i.e., subjects avoided consumption of solutions which had previously been paired with the antagonists. Stolerman *et al.* [114] suggested that the blocking by naloxone of the baseline endorphin activity was aversive. This naloxone-induced aversiveness was sufficient to condition an aversion to the novel solution.

While naloxone induced taste aversions, these aversions were evident only at high doses of naloxone, e.g., 3.2 and 10 mg/kg, intraperitoneally, doses that clearly saturate opiate receptors [30]. If aversions are produced by the blocking of opiate receptors by naloxone, it would be expected that aversions would occur even at lower doses, as long as opiate receptors were effectively blocked. Lower doses of naloxone, however, are usually ineffective in inducing aversions [41,114]. It is possible that in the design used by Stolerman *et al.* [114] 1–10 mg/kg of naloxone was aversive itself, independent of its blocking of baseline endorphin activity. Since endorphins are not tonically elevated, but elevated only in response to stress, it is possible that naloxone would be maximally aversive only if it blocked the opiate receptors when endorphin levels are high following a stress, a time when the endorphins would be modulating aversiveness. Naloxone at this point would be aversive because it would block the endorphin-mediated analgesia or attenuation of the stress, making the stress more aversive. Such a potentiation of stress by naloxone was noted in the earlier discussion on CER.

While it is unclear if the endorphins are involved in naloxone-induced taste aversions, other work on conditioned aversions more clearly illustrates an influence of endorphins in associative learning. As described, if animals are given a toxin following consumption of a novel solution, the animal subsequently avoids consumption of that solution. A wide range of pharmacological agents and other stressors are effective in conditioning such aversions. A notable exception to this range of stressors is foot-shock [11, 49, 72]. If animals are shocked following consumption of a specific solution, no conditioned aversion is acquired, i.e., animals continue to drink the novel solution. In an explanation of this failure, Riley, Zellner, and Duncan [94] suggested that when the shock is presented following consumption, the shock may modulate its own aversiveness by the stress-induced release of endorphins. The aversiveness of the shock is reduced to a level insufficient to condition an aversion.

To test this hypothesis Riley *et al.* [94] treated rats with naloxone prior to giving the animals a saccharin solution-foot-shock pairing. The subsequent aversion to saccharin in these subjects was then compared to aversions in subjects receiving a saccharin-shock pairing but who were pretreated with a control injection of distilled water. As expected, animals pretreated with distilled water and given the saccharin-shock pairing did not subsequently avoid the saccharin solution. On the other hand, animals pretreated with naloxone and given a saccharin-shock pairing avoided consumption of the saccharin solution on a subsequent exposure. With naloxone pretreatment, shock was effective in inducing a conditioned taste aversion. Riley *et al.* [94] suggested that naloxone blocked the modulating effect of the shock-induced release of endorphins. As a result, shock was sufficiently aversive to condition an aversion. The attenuated aversiveness of shock in water-pretreated subjects, however, was insufficient, as described above.

Further support for the role of endorphins in associative learning was reported by Riley *et al.* [94] in a second study on naloxone potentiation. As described, animals avoid consumption of previously-poisoned solutions. These aversions, however, are dose-dependent, such that with low doses of the toxin, conditioned aversions are often weak or not established at all. Riley *et al.* [94] suggested that a low dose of a toxin may be a sufficient stressor to release endorphins. These endorphins in turn attenuate the aversiveness of the low dose of the toxin to a level insufficient to condition an aversion, a mechanism similar to that proposed for shock. To test if weak toxins are ineffective in conditioning aversions due to this modulation by the endorphins, Riley *et al.* [94] treated rats with naloxone prior to giving them a pairing of a novel saccharin solution with a dose of lithium chloride that was too low to condition an aversion. Subjects pretreated with naloxone and given the saccharin-LiCl pairing formed a conditioned aversion to the saccharin solution, avoiding its consumption on a subsequent exposure. Animals without this naloxone pretreatment but who also received the saccharin-LiCl pairing continued to drink the saccharin solution, as did subjects receiving naloxone pretreatment, alone, or no experimental treatment. Riley *et al.* [94] concluded that the pretreatment with naloxone blocked the LiCl-induced, endorphin-mediated attenuation, thereby making the low dose of LiCl more aversive. That the stronger aversions in subjects receiving both naloxone and the saccharin-LiCl pairing is not simply a result of the summation of two weak aversive agents, i.e., naloxone and LiCl, is clear from the fact that no aversion was evident in subjects receiving either the naloxone or LiCl, alone.

This study extends the attenuating effects of endorphins beyond that of analgesia as was suggested in studies utilizing shock. That naloxone was able to potentiate the aversiveness of LiCl indicates that the endorphins may modulate aversiveness in general, not just pain transmission or affective responses to pain.

The results from the CER and conditioned taste aversion designs illustrate that endorphins may affect animal learning by attenuating the events that support conditioning, e.g., shock in CER and shock and LiCl in conditioned taste aversions. The results from the rat's preference for signaled shock were evidence that the endorphins may affect learning tasks in another way. Instead of weakening conditioning, as above, the classical conditioning compensatory release of endorphins reduced the aversiveness of shock and maintained an operant response, i.e., the preference for a specific side of a shuttlebox on which the signaled shock was presented.

One final study illustrates a further influence of endorphins on animal learning. In a series of studies, Domjan [36,37] reported if rats are treated with LiCl prior to receiving a saccharin-LiCl pairing, no conditioned aversion was acquired to the saccharin solution, i.e., prior treatment with LiCl interfered with the learning of the saccharin-LiCl association. Subjects receiving only the saccharin-LiCl pairing without the LiCl pretreatment avoided consumption of saccharin on a subsequent exposure. While there are numerous explanations for this LiCl pre-exposure [36], one recent interpretation involves the endorphins. Riley *et al.* [94] have argued that when LiCl is initially presented prior to the saccharin-LiCl pairing, the LiCl pretreatment stimulates the release of endorphins. These endorphins in turn modulate the aversiveness of the LiCl which is paired with saccharin. This attenuated aversiveness is insufficient to condition an aversion.

In a test of this explanation, Riley *et al.* [94] examined the effects of naloxone on the LiCl pre-exposure effect. Rats were given either distilled water or LiCl prior to receiving a saccharin-LiCl pairing. As expected, subjects receiving the pre-exposure to LiCl did not form an aversion to the saccharin solution, a finding consistent with the results by Domjan [36,37]. Subjects receiving distilled water prior to the saccharin-LiCl pairing formed an aversion, avoiding the saccharin solution. Two other groups received similar manipulations to the two groups described above, except each of these two groups was given an injection of naloxone between the saccharin-LiCl pairing. Of these groups injected with naloxone, the subjects of interest are those given LiCl prior to the saccharin-LiCl pairing. Unlike subjects not receiving naloxone, these subjects subsequently avoided the saccharin solution, i.e., naloxone reversed the LiCl pre-exposure effect. These results are consistent with the position that the LiCl pretreatment elicited the release of endorphins which modulated the aversiveness of the second LiCl injection, the one responsible for conditioning. Naloxone blocked this modulation such that the aversiveness of the second LiCl injection was sufficient to condition an aversion to saccharin.

Similar to the earlier discussions of endorphins and learning, these results suggest that endorphins may affect general aversiveness, and as a result, affect learning. Unlike the earlier reports, however, endorphins were elicited by a stressor not contributing directly to conditioning, e.g., the stress pretreatment. The early assessments of the role of endorphins in conditioning utilized a paradigm in which a stressor modulated its own aversiveness by the endorphins. In the final study, however, a stressor modulated the aversiveness of a subsequently-presented stressor. This conditioning paradigm parallels the typical paradigm examining stress-induced analgesia, e.g., the analgesic effect of a footshock pretreatment on tail-flinch thresholds to heat stimulation (see also [14–25]). That this conditioning paradigm parallels other designs in which the endorphins have been independently measured and in which analgesia has been directly assessed supports the postulated endorphin mediation of the LiCl pre-exposure effect.

Further evidence that pretreatment with a stressor can affect learning involving a subsequent stressor has been presented by Maier and Jackson [83]. As above, Maier and Jackson demonstrated that pretreatment with uncontrollable footshock interferes with the rat's ability to learn to avoid shock when subsequently given the opportunity. This phenomenon has been called learned helplessness and refers to the debilitating effects of shock pretreatment on subsequent avoidance learning. That the endorphins may be mediating this effect is indicated by the fact that in addition to interfering with avoidance learning, the shock pretreatment also produces analgesia (see also [47]).

In the preceding discussion, it was concluded that by modulating the general aversiveness of the unconditioned stimulus in classical conditioning, e.g., CER, signaled shock and conditioned taste aversions, the endorphins affected learning. In some cases, learning appeared weakened by the endorphins, e.g., CER and conditioned taste aversions, whereas in other situations, learning was facilitated, e.g., the preference for signaled shock. In all instances, it was suggested that the influence of the endorphins was due to their modulating or attenuating effects of aversiveness. That in all cases described naloxone reversed the effects that endorphin was said to be producing suggested further that the effects of the endorphins were mediated via an endorphin/opiate receptor complex. These conclusions regarding endorphin's analgesic effect which may be mediated via the opiate receptors are in agreement with the biochemical and behavioral results described earlier.

A final question posed by these results is in what way do the endorphins affect the general aversiveness of a specific event. When limited to the endorphins' attenuation of pain, an analgesic effect at the spinal level with descending serotonergic control has been suggested [12, 64, 66]. How the endorphins might affect the aversiveness of a toxin, however, is not readily clear. In this last section, we suggest a possible interaction of the endorphins and adrenocorticotrophic hormone (ACTH) to account for the endorphins' modulation of aversive events.

A number of researchers have speculated on the physiological basis of conditioned taste aversions [28, 29, 44, 48, 52, 70, 79–81, 92, 93, 95, 96, 100, 106]. The one explanation receiving the most attention is that a common, physiological event, i.e., ACTH, is responsible for the conditioning of taste aversions [1, 26, 27, 57, 69, 74, 90, 92, 93, 108–110]. Pharmacological agents which induce ACTH release also condition taste aversions [26,92]. In addition, many physiological manipulations which alter the rat's basal ACTH level or its ACTH response to a stressor affect conditioned taste aversions in a similar manner [57, 69, 74, 108–110].

Recent work by Jacquet [64,66] illustrates how the endorphins may affect any system in which ACTH is acting. Jacquet reports that one of the effects of the endorphins is the inhibition of ACTH's excitatory effects. She demonstrated this by injecting morphine into rats and examining the behavioral consequences. Morphine had two distinct effects. It initially produced behavioral excitation, followed rapidly by the stupor and catatonia characteristic of the opiates. Jacquet concluded that morphine mimiced ACTH at the ACTH receptor, thereby producing the behavioral excita-

tion. As morphine began to mimic the endorphins at the receptors sensitive to the endorphins, it initiated behavioral rigidity (an effect characteristic of the endorphins) as well as inhibited its own activation at the ACTH receptor via an endorphin-mediated inhibitory contact. In support of this mechanism underlying morphine's dual effects, Jacquet reported that injections of naloxone prior to the morphine injection resulted in only a behavioral excitation. Jacquet suggested that naloxone blocked the endorphin-mediated effects, i.e., naloxone reduced the catatonia and reversed the inhibition at the ACTH receptor. Behavioral excitation was evident, suggesting that the ACTH receptor, although sensitive to morphine, is not blocked by naloxone. Such a demonstration of the inhibitory control by the endorphins at a receptor sensitive to ACTH provides evidence that if ACTH is involved in the acquisition of learning or in the occurrence of a behavior, any manipulation that releases endorphins will have an effect.

As described above, ACTH may be involved in the conditioning of taste aversions. According to this account, when an animal is poisoned following consumption of a novel solution, the toxin elicits ACTH [1, 74, 118]. The association that is learned is between the taste of the solution and the change in ACTH from baseline, a condition elicited by the toxin. As clearly indicated by others, and suggested here, the release of ACTH is accompanied by the simultaneous release of the endorphins [45, 53–55, 98, 101, 102]. That is to say, the same stressor which elicits ACTH releases endorphins as well, establishing a situation in which the modulation of ACTH by the endorphins can occur.

This speculation on the manner in which the endorphins could inhibit the effects of ACTH could account for the previously-described modulation of aversions in the conditioned tatse aversion design. A toxin paired with specific solutions elicits ACTH, the stimulus associated with the taste of the solution. The toxin also elicits the endorphins, which modulate the effects of ACTH by the aforementioned inhibition, thereby reducing its own aversiveness. Weak stressors, e.g., low doses of LiCl or shock, are made even weaker by this attenuation, and as a result, these stressors do not condition aversions. Treatment with naloxone blocks this endorphin-meidated inhibition of ACTH, leaving the aversiveness of the stressor intact and sufficient to condition an aversion. While less speculative explanations have been presented for stress-induced analgesia, e.g., directly inhibiting pain transmission, the interaction of ACTH and endorphins seems possible as a basis for any stress which concomitantly releases ACTH and the endorphins.

In concluding this section, it should be noted that while ACTH and the endorphins are simultaneously released upon stress, this release is from the pituitary [45, 53–55, 98, 101, 123]. It is unclear whether this release enters the brain or is present at the CNS sites at which Jacquet suggests an ACTH/endorphin interaction may occur, i.e., the periaqueductal gray [97]. The potential for inhibition is present, however, and until it is clear that the brain levels of ACTH and endorphins do not change in response to stress, such an interaction is possible.

The present paper has attempted to review the current research assessing the role of the endorphins in animal learning. As described, in at least several designs, endorphins clearly influence the strength of learning. In each instance in which the endorphins appeared to affect learning, the effect was that of attenuating the aversiveness of the stimulus event supporting conditioning. In addition, naloxone reversed each of the postulated effects of the endorphins. The data from these conditioning and learning experiments offer support to the biochemical and behavioral research on the analgesic effects and the physiological substrate of the endorphins.

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REFERENCES

1. Ader, R. Conditioned adrenocortical steroid elevations in the rat. *J. comp. physiol. Psychol.* **90:** 1156–1163, 1964.
2. Akil, H., I. Madden, R. Patrick and J. 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. Kosterlitz. Amsterdam: Elsevier/North Holland, 1976, pp. 63–70.
3. Akil, H., D. Richardson, J. Hughes and J. Barchas. Enkephalin-like material elevated in ventricular cerebrospinal fluid of pain patients after analgetic focal stimulation. *Science* **201:** 463–465, 1978.
4. Akil, H., S. Watson, P. Berger and J. Barchas. Endorphins, B-LPH, and ACTH: Biochemical, pharmacological, and anatomical studies. In: *The Endorphins,* edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 125–137.
5. Amir, S. and Z. Amit. Endogenous opioid ligands may mediate stress-induced changes in the affective properties of pain related behavior in rats. *Life Sci.* **23:** 1143–1152, 1978.
6. 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.
7. Badia, P., J. Marsh, C. Coker and B. Abbott. Choice and the dependability of stimuli that predict shock and safety. *J. exp. Analysis Behav.* **26:** 95–111, 1976.
8. Barker, J. and T. Smith (editors). *The Role of Peptides in Neuronal Function.* Abstracts of the International Peptide Symposium, Bethesda, Maryland, 1979.
9. Bella, D., F. Casacci and A. Sassi. Opiate receptors: Different ligand affinity in various brain regions. In: *The Endorphins,* edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 271–277.
10. Belluzzi, J., N. Grant, V. Garsky, D. Sarantakis, C. Wise and L. Stein. Analgesia induced in vivo by central administration of enkephalin in rat. *Nature* **260:** 625–626, 1976.
11. Berk, A. and R. Miller. LiCl-induced aversions to audiovisual cues as a function of response measure and CS-US interval. *Behav. Biol.* **24:** 185–208, 1978.
12. Blair, R., P. Cytryniak, P. Shizgal and Z. Amit. Naloxone's antagonism of rigidity but not explosive motor behavior: Possible evidence for two types of mechanisms underlying the actions of opiates and opioids. *Behav. Biol.* **24:** 24–31, 1978.

13. Bloom, F., J. Rossier, E. Battenberg, A. Bayon, E. French, S. Henrickson, G. Siggins, D. Segal, R. Browne, N. Ling and R. Guillemin. B-endorphin: Cellular localization, electrophysiological and behavioral effects. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 271–277.
14. Bodnar, R., D. Kelly and M. Glusman. Stress-induced analgesia: Time course of pain reflex alternations following cold water swims. *Bull. Psychon. Soc.* **11:** 333–336, 1978.
15. Bodnar, R., D. Kelly and M. Glusman. 2-deoxy-D-glucose analgesia: Influences of opiate and non-opiate factors. *Pharmac. Biochem. Behav.* **11:** 297–302, 1979.
16. Bodnar, R., 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.
17. Bodnar, R., D. Kelly, A. Mansour and M. Glusman. Differential effects of hypophysectomy upon analgesia induced by two glucoprivic stressors and morphine. *Physiol. Behav.*, in press.
18. Bodnar, R., D. Kelly, A. Spiaggia and M. Glusman. Stress-induced analgesia: Adaptation following chronic cold-water swims. *Bull. Psychon. Soc.* **11:** 337–340, 1978.
19. Bodnar, R., D. Kelly, A. Spiaggia and M. Glusman. Biphasic alterations of nociceptive thresholds induced by food deprivation. *Physiol. Psychol.*, in press.
20. Bodnar, R., D. Kelly, S. Steiner and M. Glusman. Stress-produced analgesia and morphine-produced analgesia: Lack of cross-tolerance. *Pharmac. Biochem. Behav.* **8:** 661–666, 1978.
21. Bodnar, R., M. Glusman, M. Brutus, A. Spiaggia and D. Kelly. Analgesia induced by cold-water stress: Attenuation following hypophysectomy. *Physiol. Behav.* **23:** 53–62, 1979.
22. Bodnar, R., M. Glusman, A. Spiaggia, M. Brutus and D. Kelly. Attenuation of stress-induced increases in nociceptive thresholds by hypophysectomy. *Second World Congress on Pain*, Montreal, Canada, 1978.
23. Bodnar, R., 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.
24. Bodnar, R., 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.
25. Bodnar, R., D. Kelly, A. Spiaggia, C. Pavlides and M. Glusman. Stress-induced analgesia: Effect of naloxone following cold water swims. *Bull. Psychon. Soc.* **12:** 125–128, 1978.
26. Braveman, N. What studies on pre-exposure to pharmacological agents tell us about the nature of the aversion-inducing agent. In: *Learning Mechanisms in Food Selection*, edited by L. Barker, M. Best and M. Domjan. Waco: Baylor University Press, 1977, pp. 511–530.
27. Braveman, N. The role of blocking and compensatory conditioning in the treatment pre-exposure effect. *Psychopharmacology* **61:** 177–189, 1979.
28. Brown, Z., Z. Amit, B. Smith and G. Rockman. Disruption of taste aversion learning by pretreatment with diazepam and morphine. *Pharmac. Biochem. Behav.* **10:** 17–21, 1979.
29. Bures, J. and O. Buresova. Physiological mechanisms of conditioned food aversion. In: *Food Aversion Learning*, edited by N. Milgram, L. Krames and T. Alloway. New York: Plenum Press, 1978, pp. 219–255.
30. Chance, W. Autoanalgesia: Endogenous mechanisms of pain control. *East. Psychol. Ass.* **Philadelphia, Pennsylvania, 1979.**
31. Chance, W., G. Krynock and J. Rosecrans. Antinociception following lesion-induced hyperemotionality and conditioned fear. *Pain* **4:** 243–252, 1978.
32. Chance, W., A. White, G. Krynock and J. Rosecrans. Autoanalgesia: Behaviorally-activated antinociception. *Eur. J. Pharmac.* **44:** 283–284, 1977.
33. Chance, W., A. White, G. Krynock and J. Rosecrans. Conditional fear-induced antinociception and decreased binding of (^{3}H)N-Leu-enkephalin to rat brain. *Brain Res.* **141:** 371–374, 1978.
34. Colelli, B. and S. Sparber. Differential effect of naloxone on fixed ratio operant behavior in stressed and non-stressed rats. *Pharmacologist* **19:** 139, 1977.
35. de Weid, D., B. Bohus, J. van Ree and I. Urban. Behavioral and electrophysiological effects of peptides related to lipotrophin (B-LPH). *J. Pharmac. exp. Ther.* **204:** 570–580, 1978.
36. Domjan, M. Effects of proximal unconditioned stimulus preexposure on ingestional aversions learned as a result of taste presentation following drug treatment. *Anim. Learn. Behav.* **6:** 133–142, 1978.
37. Domjan, M. and M. Best. Paradoxical effects of proximal unconditioned stimulus pre-exposure: Interference with and conditioning of a taste aversion. *J. exp. Psychol. Anim. Behav. Proc.* **3:** 310–321, 1977.
38. Ehrenpreis, S., R. Balagot, J. Comathy and S. Myles. Naloxone reversible analgesia in mice produced by inhibitors of enkephalin metabolism. *Second World Congress on Pain*, Montreal, Canada, 1978.
39. Fanselow, M. Naloxone attenuates rats preference for signaled shock. *Physiol. Psychol.* **7:** 70–74, 1979.
40. Foley, K., R. Kaiko, C. Inturrisi, J. Posner, C. Li and R. Moude. Intravenous and intraventricular administration of beta-endorphin in man: Preliminary studies. *Second World Congress on Pain*, Montreal, Canada, 1978.
41. Frenk, H. and G. Rogers. The suppressant effects of naloxone on food and water intake in the rat. *Behav. Neurol. Biol.*, in press.
42. Gainer, H. (editor). *Peptides in Neurobiology*. New York: Plenum Press, 1977.
43. Garcia, J. and F. Ervin. Gustatory-visceral and telereceptor-cutaneous conditions: Adaptation in internal and external milieus. *Communs. behav. Biol.* **1:** 389–415, 1968.
44. Gaston, K. Brain mechanisms of conditioned taste aversion learning: A review of the literature. *Physiol. Psychol.* **6:** 340–353, 1978.
45. Gentleman, S., M. Ross, L. Lowney, B. Cox and A. Goldstein. Pituitary endorphins. In: *Opiates and Endogenous Opioid Peptides*, edited by H. Kosterlitz. Amsterdam: Elsevier/North Holland, 1976, pp. 27–34.
46. Goldstein, A., G. Pryor, L. Otis and F. Larsen. On the role of endogenous opioid peptides: Failure of naloxone to influence shock escape threshold in the rat. *Life Sci.* **18:** 599–604, 1976.
47. Gorelick, D., D. Catlin, R. George and C. Li. Beta-endorphin is behaviorally active in rats after chronic intravenous administration. *Pharmac. Biochem. Behav.* **9:** 385–386, 1978.
48. Goudie, A., E. Thornton and J. Wheatley. Attenuation by alpha-methyltyrosine of an amphetamine induced conditioned taste aversion in rats. *Psychopharmacologia* **45:** 119–123, 1975.
49. Green, L., A. Bouzas and H. Rachlin. Test of an electric-shock analog to illness-induced aversion. *Behav. Biol.* **7:** 513–518, 1972.
50. Grevert, P. and A. Goldstein. Some effects of naloxone on behavior in the mouse. *Psychopharmacology* **53:** 111–113, 1977.
51. Grevert, P. and A. Goldstein. Endorphins: Naloxone fails to alter experimental pain or mood in humans. *Science* **199:** 1093–1095, 1978.
52. Grupp, L. Effects of pimozide on the acquisition, maintenance, and extinction of an amphetamine-induced taste aversion. *Psychopharmacology* **53:** 235–242, 1977.
53. Guillemin, R. Beta-lipotropin and endorphins: Implications of current knowledge. *Hosp. Pract.* **13:** 53–60, 1978.
54. 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.

55. Guillemin, R., F. Bloom, J. Rossier, S. Minick, S. Hendricksen, R. Burgus and N. Ling. Current physiological studies with the endorphins. In: *Molecular Endocrinology*, edited by M. Szelke. Amsterdam: Elsevier/North Holland, 1977, pp. 251–267.
56. Hayes, R., G. Bennett, P. Newlon and D. Mayer. Behavioral and physiological studies of non-narcotic analgesia in the rat elicited by certain environmental stimuli. *Brain Res.* **155:** 69–90, 1978.
57. Hennessy, J., W. Smotherman and S. Levine. Conditioned taste aversion and the pituitary-adrenal system. *Behav. Biol.* **16:** 413–424, 1976.
58. Holaday, J., H. Loh and C. Li. Unique behavioral effects of B-endorphin and their relationship to thermoregulation and hypothalamic function. *Life Sci.* **22:** 1525–1536, 1978.
59. Holaday, J., E. I., H. Loh and C. Li. Endorphins may function in heat adaptation. *Proc. natn. Acad. Sci. U.S.A.* **75:** 2923–2927, 1978.
60. Hosobuchi, Y. and C. Li. A demonstration of the analgesic activity of human B-endorphin in six patients. *Second World Congress on Pain*, Montreal, Canada, 1978.
61. Hosobuchi, Y., J. Rossier, F. Bloom and R. Guillemin. Stimulation of human periaqueductal gray for pain relief increases immunoreactive B-endorphin in ventricular fluid. *Science* **203:** 279–281, 1979.
62. Hughes, J. Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Res.* **88:** 295–309, 1975.
63. Jacob, J., E. Tremblay and M. Colombel. Facilitation de reactions nociceptives par la naloxone chez la souris et chez le rat. *Psychopharmacologia* **37:** 217–223, 1974.
64. Jacquet, Y. Opiate effects after adrenocorticotropin or B-endorphin injection in the periaqueductal gray matter of rats. *Science* **201:** 1032–1034, 1978.
65. Jacquet, Y., N. Marks and C. Li. Behavioral and biochemical properties of "opioid" peptides. In: *Opiates and Endogenous Opioid Peptides*, edited by H. Kosterlitz. Amsterdam: Elsevier/North Holland, 1976, pp. 411–414.
66. Jacquet, Y., W. Klee, K. Rice, I. Iijima and J. Minamikawa. Stereospecific and nonstereospecific effects of (+) - and (−) - morphine: Evidence for a new class of receptors. *Science* **198:** 842–845, 1977.
67. Johansson, O., T. Hokfelt, R. Elde, M. Schultzberg and L. Terenius. Immunohistochemical distribution of enkephalin neurons. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 51–70.
68. Katz, R. and J. Gelbart. Endogenous opiates and behavioral responses to environmental novelty. *Behav. Biol.* **24:** 338–348, 1978.
69. Kendler, K., J. Hennessy, W. Smotherman and S. Levine. An ACTH effect on recovery from conditioned taste aversion. *Behav. Biol.* **17:** 225–229, 1976.
70. Kolb, B., A. Noneman and P. Abplanalp. Studies on the neural mechanisms of baitshyness in rats. *Bull. Psychon. Soc.* **10:** 389–392, 1977.
71. Kosterlitz, H. and J. Hughes. Development of the concepts of opiate receptors and their ligands. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 31–44.
72. Krane, R. and A. Wagner. Taste aversion learning with a delayed shock US: Implications for the "generality of the laws of learning." *J. comp. physiol. Psychol.* **88:** 882–889, 1975.
73. Levine, J., N. Gordon and H. Fields. Evidence that the analgesic effect of placebo is mediated by endorphins. *Second World Congress on Pain*, Montreal, Canada, 1978.
74. Levine, S., W. Smotherman and J. Hennessy. Pituitary-adrenal hormones and learned taste aversion. In: *Neuropeptide Influences on the Brain and Behavior*, edited by L. Miller, C. Sandman and A. Kastin. New York: Raven Press, 1977, pp. 163–177.
75. Lewis, J., J. Cannon, S. Ryan and J. Liebeskind. Behavioral pharmacology of opioid peptides. *The Role of Peptides in Neuronal Function*. Bethesda, Maryland, 1979.
76. Liebeskind, J. and L. Paul. Psychological and physiological mechanisms of pain. *A. Rev. Psychol.* **28:** 41–60, 1977.
77. Lindblom, V. and R. Tegner. Is the endorphin system operative in clinical pain states? Morphine antagonism in chronic pain patients. *Second World Congress on Pain*, Montreal, Canada, 1978.
78. Lord, J., A. Waterfield, J. Hughes and H. Kosterlitz. Multiple opiate receptors. In: *Opiates and Endogenous Opioid Activity*, edited by H. Kosterlitz. Amsterdam: Elsevier/North Holland, 1976, pp. 275–280.
79. Lorden, J. and D. Margules. Enhancement of conditioned taste aversions by lesions of the midbrain raphe nuclei that deplete serotonin. *Physiol. Psychol.* **5:** 273–279, 1977.
80. Lorden, J. and G. Oltmans. Alteration of the characteristics of learned taste aversion by manipulation of serotonin levels in the rat. *Pharmac. Biochem. Behav.* **8:** 13–18, 1978.
81. Lorden, J., M. Callahan and R. Dawson. Effects of forebrain serotonin depletion on fenfluramine-induced taste aversions. *Physiol. Psychol.* **7:** 97–101, 1979.
82. Madden, J., H. Akil, R. Patrick and J. Barchas. Stress-induced parallel changes in central opioid levels and pain responsiveness in the rat. *Nature* **265:** 358–360, 1977.
83. Maier, S. and R. Jackson. Learned helplessness: All of us were right (and wrong): Inescapable shock has multiple effects. In: *Psychology of Learning and Motivation*, edited by G. Bower. New York: Academic Press, in press.
84. Martin, W., G. Eades, J. Thompson, R. Huppler and P. Gilbert. The effects of morphine- and nalorphine-like drugs in the non dependent and morphine-dependent chronic spinal dog. *J. Pharmac. exp. Ther.* **197:** 517–532, 1976.
85. Mihic, D. and E. Binkert. Is placebo analgesia mediated by endorphin? *Second World Congress on Pain*, Montreal, Canada, 1978.
86. North, M. Naloxone reversal of morphine analgesia but failure to alter reactivity to pain in the formalin test. *Life Sci.* **22:** 295–302, 1978.
87. Pert, A., R. Simantov and S. Snyder. A morphine-like factor in mammalian brain: Analgesic activity in rats. *Brain Res.* **136:** 523–533, 1977.
88. Pilcher, C. and I. Stolerman. Recent approaches to assessing opiate dependence in rats. In: *Opiates and Endogenous Opioid Peptides*, edited by H. Kosterlitz. Amsterdam: Elsevier/North Holland, 1976, pp. 327–334.
89. Pilcher, C., I. Stolerman and G. D'Mello. Aversive effects of narcotic antagonists in rats. In: *Characteristics and Functions of Opioids*, edited by R. Van Ree and L. Terenius. Amsterdam: Elsevier/North Holland, 1978, pp. 437–438.
90. Rigter, H. and A. Popping. Hormonal influences on the extinction of conditioned taste aversion. *Psychopharmacologia* **46:** 255–261, 1976.
91. Riley, A. and C. Clarke. Conditioned taste aversions: A bibliography. In: *Learning Mechanisms in Food Selection*, edited by L. Barker, M. Best and M. Domjan. Waco: Baylor University Press, 1977, pp. 593–616.
92. Riley, A., W. Jacobs and V. LoLordo. Drug exposure and the acquisition and retention of a conditioned taste aversion. *J. comp. physiol. Psychol.* **90:** 799–807, 1976.
93. Riley, A., W. Jacobs and V. LoLordo. Morphine-induced taste aversions: A consideration of parameters. *Physiol. Psychol.* **6:** 96–100, 1978.
94. Riley, A., D. Zellner and H. Duncan. The effect of naloxone pretreatment on the acquisition of conditioned taste aversions: A role for endogenous opiates. *East. Psychol. Ass.* Philadelphia, Pennsylvania, 1979.
95. Roberts, D. and H. Fibiger. Attenuation of amphetamine-induced taste aversion following intraventricular 6-hydroxydopamine. *Neurosci. Lett.* **1:** 343–347, 1975.

96. Roberts, D. and H. Fibiger. Lesions of the dorsal noradrenergic projection attenuate morphine-, but not amphetamine-induced conditioned taste aversion. *Psychopharmacology* **55:** 183–186, 1977.
97. Rossier, J., E. French, C. Rivier, N. Ling, R. Guillemin and F. Bloom. Foot-shock induced stress increases B-endorphin levels in blood but not brain. *Nature* **270:** 618–620, 1977.
98. Santagostino, A., D. Cocchi, G. Giagnoni, E. Gori. E. Muller and S. Ferri. Some relationships between endorphins and pituitary hormones. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 175–181.
99. Schull, J. A conditioned opponent theory of pavlovian conditioning and habituation. In: *The Psychology of Learning and Motivation*, edited by G. Bower. New York: Academic Press, in press.
100. Sessions, G., G. Kant and G. Koob. Locus coeruleus lesions and learning in the rat. *Physiol. Behav.* **17:** 853–859, 1976.
101. Shanker, G. and R. Sharma. Beta-endorphin stimulates corticosterone synthesis in isolated rat adrenal cells. *Biochem. biophys. Res. Commun.* **86:** 1–5, 1979.
102. Sherman, J. and J. Liebeskind. An endorphinergic, centrifugal substrate of pain modulation: Recent findings, current concepts, and complexities. *Proceedings of the Association for Research in Nervous and Mental Disease*, in press.
103. Siegel, S. Morphine tolerance acquisition as an associative process. *J. exp. Psychol. Anim. Behav. Proc.* **3:** 1–13, 1977.
104. Siegel, S. The role of conditioning in drug tolerance and addiction. In: *Psychopathology in Animals*, edited by J. Keehn. New York: Academic Press, in press.
105. Siegel, S. Tolerance to the hyperthermic effect of morphine in the rat is a learned response. *J. comp. physiol. Psychol.*, in press.
106. Sklar, L. and Z. Amit. Manipulations of catecholamine systems block conditioned taste aversion induced by self-administered drugs. *Neuropharmacology* **16:** 644–655, 1977.
107. Smith, T., J. Hughes, H. Kosterlitz and R. Sosa. Enkephalins: isolation, distribution and function. In: *Opiates and Endogenous Opioid Peptides*. Amsterdam: Elsevier/North Holland, 1976, pp. 57–62.
108. Smotherman, W. and S. Levine. ACTH and $ACTH_{4-10}$ modification of neophobia and taste aversion responses in the rat. *J. comp. physiol. Psychol.* **92:** 22–33, 1978.
109. Smotherman, W., J. Hennessy and S. Levine. Plasma corticosterone levels during recovery from LiCl produced taste aversions. *Behav. Biol.* **16:** 401–402, 1976.
110. Smotherman, W., J. Hennessy and S. Levine. Plasma corticosterone levels as an index of the strength of illness induced taste aversions. *Physiol. Behav.* **17:** 903–908, 1976.
111. Snyder, S. Overview of some new peptide research. *The Role of Peptides in Neuronal Function*. Bethesda, Maryland, 1979.
112. Snyder, S. and S. Matthysee. *Opiate Receptor Mechanisms*. Cambridge: MIT Press, 1975.
113. Spiaggia, A., R. Bodnar, 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.
114. Stolerman, I., C. Pilcher and G. D'Mello. Stereospecific aversive properties of narcotic antagonists in morphine-free rats. *Life Sci.* **22:** 1755–1762, 1978.
115. Terenius, L. Endorphin mechanisms in chronic pain. *Second World Congress on Pain*, Montreal, Canada, 1978.
116. Terenius, L. Significance of endorphins in endogenous antinociception. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 321–332.
117. Walker, J., C. Sandman, G. Berntson, R. McGivern, D. Coy and A. Kastin. Endorphin analogs with potent and long-lasting analgesic effects. *Pharmac. Biochem. Behav.* **7:** 543–548, 1977.
118. Watson, B. and A. Riley. Effect of lithium chloride and morphine sulfate on plasma corticosterone levels in the rat. *Can. Psychol. Ass.* Toronto, Ontario, 1976.
119. Watson, S., H. Akil, C. Richard and J. Barchas. Evidence for two separate opiate peptide neuronal systems. *Nature* **275:** 226–228, 1978.
120. Yaksh, T. Central nervous system sites mediating opiate analgesia. *Second World Congress on Pain*, Montreal, Canada, 1978.
121. Yaksh, T. Opiate receptors for behavioral analgesia resemble those related to the depression of spinal nociceptive neurons. *Science* **199:** 1231–1233, 1978.
122. Yang, H., J. Hong, W. Fratta and E. Costa. Rat brain enkephalins: Distribution and biosynthesis. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 149–159.
123. Yoshimi, H., S. Matsukura, S. Sueoka, M. Fukase, M. Yokota, Y. Hirata and H. Imura. Radioimmunoassay for B-endorphin: Presence of immunoreactive "big-big" B-endorphin ("big" B-lipotropin) in human and rat pituitaries. *Life Sci.* **22:** 2189–2196, 1978.
124. Zetler, G. Active peptides in the nervous tissue: Historical prospects. In: *The Endorphins*, edited by E. Costa and M. Trabucchi. New York: Raven Press, 1978, pp. 1–21.