the behavior seen during opiate withdrawal, we cannot accept the notion, implied by Jacquet’s formulation, that the only compounds that can induce opiate-like dependence are those that can also produce EMB, and that an ACTH receptor is critically involved in this effect.

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References and Notes
4. Wei and Loh, have used cannula with an outer diameter of 0.81 mm. Jacquet, in her study, used cannula with an outer diameter of 0.8 mm.

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The objection of Amir et al. to Jacquet’s formulation (1) of a dual mechanism mediating opiate effects, with the endorphin receptor mediating narcotic analgesia-catatonia, and the adrenocorticotropic hormone (ACTH) receptor mediating opiate excitation and abstinence behavior, appear to center on the ACTH receptor. Their criticisms of this latter mechanism fall into two categories:

1) The occurrence of explosive motor behavior (EMB) after periaqueductal gray (PAG) injections of beta-endorphin (2), or intracerebroventricular (ICV) injections of compounds other than opiates or ACTH (lithium or calcium chelators), and the nonoccurrence of EMB after ICV injections of some opiates such as levorphanol and etonitazene.

2) Some in vitro (3) and in vivo (4, 5) effects of ACTH that appear to be at variance with the view of a receptor other than the endorphin receptor that mediates some of morphine’s actions.

I deal here with these points in this sequence.

1) To date, there is only one report (2) on the dependence liability of beta-endorphin after direct, chronic administration to the brain. (The direct route to brain is necessary since it is not yet established that this peptide can cross the blood-brain barrier as an intact peptide.) In this investigation, it is not clear whether the infused peptide was actually the intact, or an altered form of beta-endorphin since the subcutaneously implanted osmotic mini-pump, maintained at body temperature, served as the reservoir for beta-endorphin over the 70-hour infusion period. Moreover, considering the large size of the intracerebral cannula (outer diameter, 0.81 mm), it is probable that the site of infusion may have overlapped with the aqueduct or fourth ventricle, thereby allowing the injected peptide to diffuse to other central nervous system (CNS) sites through the ventricular fluid. These possible sources of error may explain why abstinence signs (abnormal posture, ear blanching, licking, and ptosis) occurred during the period of infusion, although the authors attribute the reason to be the short interval between surgery and experimentation (which may have been another source of error).

The argument concerning the occurrence or nonoccurrence of EMB following the ICV injection of various compounds fails to make an important distinction between ICV and PAG injections. The former is nonspecific with respect to site, and therefore mechanism of action (that is, the CNS site or sites which mediate the behavioral effects remain unidentified and can be any site adjacent to the ventricles), while the latter is specific, and more to the point, specific to the site where morphine exerts its effects of analgesia-catatonia and EMB. I have previously reported (6) that PAG injections of some opiates (methadone, levorphanol, etorphine) failed to result in EMB, and only high doses of these agents were able to achieve a mild degree of analgesia. This was seen as due to the high lipophilicity of these opiates which allowed rapid diffusion throughout the CNS. This diffusion, at the same time, activated those CNS sites which exerted an inhibitory influence on the excitatory action of the opiate at the ACTH receptor. In this way, some opiates with high dependence liability fail to cause EMB when injected into the PAG, while the low lipophilicity of morphine allows local effects at the PAG to be expressed.

2) That ACTH(1-24) at 10^-6M competitively displaced [3H]dihydromorphine from binding sites in brain (3) is not incompatible with the view that morphine effects are mediated by two receptors, a speciesspecific endorphin receptor, and a nonstereospecific ACTH receptor. Moreover, since ACTH has opposite effects from endorphin, it is not surprising that ACTH can antagonize morphine analgesia (mediated by the endorphin receptor (4)).

Excessive grooming induced by ICV injection of ACTH (5) may have been due to a degradation product of ACTH, since this peptide is known to undergo rapid degradation in brain. Naloxone antagonism of this effect may have been mediated by a nonopiate mechanism, since naloxone has been reported to antagonize the effects of nitrous oxide, gamma-aminobutyric acid, acetylcholine, and so on.

In view of the finding (8) that both beta-endorphin and ACTH are derived from the same "31 k" precursor, it is not unreasonable to assume that these two peptides have correlated functions in the regulation of behavior.

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References and Notes
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