The physiological activity of neurons requires energy derived from the metabolism of glucose. The mapping and quantification of regional glucose utilization rates by the 2-deoxy-D-[1-14C] glucose is a method that provides an index of regional functional activity in the central nervous system. This method has been used to investigate the functional cerebral anatomy of both spontaneous and naloxone-precipitated morphine withdrawal. A selective and highly reproducible enhancement on rates of glucose utilization was found during morphine withdrawal. The regional distribution of this elevated metabolic activity was similar during spontaneous and naloxone-precipitated withdrawal, but a smaller magnitude of changes overall was observed in spontaneous withdrawal that could reflect its reduced behavioral intensity compared to precipitated withdrawal. The hypermetabolism was primarily produced in thalamic and limbic areas, particularly the central nucleus of amygdala. Several hypothalamic nuclei, including the posterior nucleus, the paraventricular nucleus and the lateral area, showed increased metabolic activity. Other midbrain regions, such as locus coeruleus, ventral tegmental area, dorsal parabrachial nucleus, superior colliculus, dorsal tegmental nucleus and median raphe, also increased their glucose utilization rates. Cortical areas (except visual and olfactory cortices) and hindbrain (excluding cerebellar vermis) were almost unaffected. Low doses of naloxone (0.5 μg/kg) insufficient to produce severe behavioral signs of withdrawal in...
dependent rats were able to increase rates of glucose utilization in the thalamic nuclei and certain brain stem structures such as the interpeduncular nucleus. The enhancement in metabolic activity during morphine abstinence was found in many noradrenergic structures in agreement with previous results obtained after local administration of opiate antagonists and c-fos mapping, suggesting the involvement of the noradrenergic system in opiate dependency and withdrawal. In addition, during precipitated morphine withdrawal, an increased glucose utilization was found in the superficial layers of the dorsal horn in the cervical and thoracic spinal cord. This hypermetabolism could be due to an increased input from small diameter primary afferent fibers, and it supports the hypothesis that the enhanced neuronal activity in superficial layers of the spinal cord participates in the manifestation of opioid withdrawal.

Acute and chronic morphine exposure has been reported to induce effects opposite those of morphine withdrawal, i.e., a decrease in the rate of glucose utilization in some selective brain structures. Thus, acute morphine exposure produces metabolic decreases in several thalamic nuclei, whereas chronic treatment diminishes glucose utilization in cortical regions. Early studies, however, reported a small increase in metabolism in chronically morphine-treated rats and a return toward control during withdrawal in some brain regions such as dorsal hippocampus, entorhinal cortex and subiculum. The discrepancies could be due to the appearance of opioid withdrawal in chronically morphine-treated animals since rates of glucose utilization were measured some hours after the removal of morphine pellets in this study.

The increased brain rates of glucose utilization during naloxone-precipitated morphine withdrawal have been reported to be reduced by compounds that are able to attenuate the behavioral expression of morphine abstinence, such as the $\alpha_2$-agonist clonidine. This effect is a widespread phenomenon that affects brain regions containing high densities of $\alpha_2$-receptors, mainly hypothalamic nuclei and limbic areas, and other structures with very low densities of these receptors. However, the distribution of the metabolic responses to specific drugs is usually not related simply to the presence of relevant receptors but also reflects the influence of affer-