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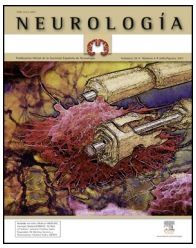

REVIEW ARTICLE

Effects of morphine on brain plasticity☆

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KEYWORDS
Morphine;
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Abstract
Introduction: Morphine shares with other opiates and drugs of abuse the ability to modify the plasticity of brain areas that regulate the morphology of dendrites and spines, which are the primary sites of excitatory synapses in regions of the brain involved in incentive motivation, rewards, and learning.
Objective: In this review we discuss the impact of morphine use during the prenatal period of brain development and its long-term consequences in murines, and then link those consequences to similar effects occurring in human neonates and adults.
Development: Repeated exposure to morphine as treatment for pain in terminally ill patients produces long-term changes in the density of postsynaptic sites (dendrites and spines) in sensitive areas of the brain, such as the prefrontal cortex, the limbic system (hippocampus, amygdala), and caudate nuclei and nucleus accumbens. This article reviews the cellular mechanisms and receptors involved, primarily dopaminergic and glutamatergic receptors, as well as synaptic plasticity brought about by changes in dendritic spines in these areas.
Conclusions: The actions of morphine on both developing and adult brains produce alterations in the plasticity of excitatory postsynaptic sites of the brain areas involved in limbic system functions (reward and learning). Doctors need further studies on plasticity in dendrites and spines and on signalling molecules, such as calcium, in order to improve treatments for addiction.

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PALABRAS CLAVE
Morfina;
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Receptores opiáceos

Efectos de la morfina en la plasticidad cerebral

Resumen
Introducción: La morfina, como otros opiáceos y las drogas de abuso, tiene la capacidad de modificar la plasticidad cerebral de las áreas que regulan la morfología neuronal de las dendritas y espinas, que son el sitio primario de sinapsis excitatorias en regiones cerebrales que regulan funciones de incentivo motivación, recompensa y aprendizaje.
Objetivo: En la presente revisión se analizan aspectos del impacto del uso de la morfina durante los periodos prenatales del desarrollo cerebral y las consecuencias a largo plazo en murinos, para relacionar estos efectos que ocurren en el humano neonato y adulto.
Desarrollo: La exposición repetida a la morfina en el tratamiento del dolor en enfermos terminales produce cambios a largo plazo en la densidad postsináptica de sitios (dendritas y espinas) en áreas sensibles del cerebro, como la corteza prefrontal y el sistema límbico (hipocampo, amígdala), así como en los núcleos caudado y accumbens. Este artículo revisa los mecanismos celulares implicados, principalmente de los receptores dopaminérgicos y glutamatérgicos, así como la plasticidad sináptica lograda por los cambios en las dendritas y espinas en esta área.
Conclusiones: Las acciones de la morfina durante el desarrollo del cerebro y también en el cerebro adulto producen alteraciones en la plasticidad de sitios excitatorios postsinápticos, áreas del cerebro que están implicadas en las funciones del sistema límbico (la recompensa y el aprendizaje). Se necesitan más estudios sobre la plasticidad en las dendritas y espinas en sus moléculas de señalización, tales como el calcio, con el fin de mejorar el tratamiento de la adicción.

Introduction

Opiate analgesics (morphine, codeine, etc.) have a long history of clinical use in the treatment of chronic pain. Recently, endogenous opioids have been found in the neurons of brain regions associated with nociceptive response. When used recreationally, however, these drugs are very often taken in excess and affect users' behaviour, which creates a serious social problem found across the globe. Opioids activate 3 types of receptors (mu, delta, and kappa) in the dopaminergic system. This mainly affects the nucleus accumbens (NAc), which undergoes changes in density of the dendritic spines (postsynaptic sites where receptors are located). The above process also affects the plasticity of the dendritic spines during nervous system development. In adults, this feature is crucial for addictive effects and other behaviours (fear, decision-making) to become ingrained.

Development

There are several theories explaining how a person reaches a state of addiction. According to the French philosopher Deleuze, addictions are situational and interactional processes that alter the body, simultaneously changing the production of desire and life itself.[1] Other sources express a neurobiological approach and point to long-term changes in different neural systems due to exposure to drugs.[2] The incentive sensitisation theory of addiction holds that exposure to a substance intensifies signalling in reward system circuits, a phenomenon echoed by the subject's behaviour.[3] This may depend on the route of administration of the drug.[2]

The most commonly employed drugs include such opiates as morphine, which is widely abused in the United States,[4] Mexico,[5] and other countries. Morphine addiction manifests as a chronic disorder affecting behaviour. The learned associations that develop between the substance consumed and the context in which consumption occurs result in sensitisation, and it seems that this sensitisation to the substance is provoked by conditioned behaviour processes.[6] Back et al.[7] reported sex differences in use of opioid medications, stating that they were more frequently prescribed to men than women (91.7% vs 77.8%); furthermore, men used them together with alcohol. Although more women than men stockpiled non-prescribed drugs in order to increase their efficacy against pain (38.8% vs 20.0%), their drug consumption was also associated with behavioural changes. Opioids have been employed in treating numerous signs and symptoms, including pain, diarrhoea, and cough. These substances have also been used to provoke the subjective effects, which have contributed to their abuse. This has given rise to an extremely serious social problem found worldwide. The therapeutic and subjective effects of opiates point to activation of an endogenous system and the receptors specific to these substances, which are distributed throughout the central and peripheral nervous systems.[8]

Morphine structure and opiate receptors

The chemical structure of morphine (the phenanthrene alkaloid of opium), and of its metabolic derivatives, determines the effects observed at the clinical level (analgesia and side effects), and the substance's ability to cross the blood-brain barrier. Its main derivatives, morphine-6-glucuronide and morphine-3-glucuronide, are