Neurología. 2015;30(3):176—180

NEUROLOGÍA

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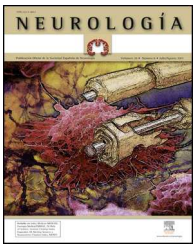

REVIEW ARTICLE

Effects of morphine on brain plasticity☆

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Received 7 July 2014; accepted 8 August 2014
Available online 5 March 2015

KEYWORDS
Morphine;
Dendritic spines;
Brain plasticity;
Opiate receptors

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.

☆ Please cite this article as: Beltrán-Campos V, Silva-Vera M, García-Campos ML, Díaz-Cintra S. Efectos de la morfina en la plasticidad cerebral. Neurología. 2015;30:176-180.

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PALABRAS CLAVE
Morfina;
Espinas dendríticas;
Plasticidad cerebral;
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

highly hydrophilic. However, morphine-6-glucuronide is the only type able to penetrate the blood-brain barrier, and its analgesic effect is therefore more potent than the effects of the parent drug or morphine-3-glucuronide.[9] Rat studies by Mayer and Liebeskind[10] found that electrical stimulation of the periventricular and central grey matter, and of parts of the midbrain, provoked deep analgesia. This state could be reversed using naloxone (an opioid antagonist). This naloxone-sensitive response involves the release of opioid derivatives (enkephalins and endorphins) that are endogenous to the brain.[11] The 3 recognised families of opioid receptors are mu, delta, and kappa; of these 3, mu receptors are clinically important since they are linked to the action of morphine.[12] The mu opioid receptor (MOR) is classified among the G-protein coupled receptors. In humans, these receptors have been associated with various side effects of opiate consumption, including respiratory system changes and opiate addiction.[13,14] In 2013, Perez-Aguilar et al.[15] presented their computational design of the expression and description of a water-soluble variant of a G-protein coupled receptor, specifically the MOR, which is involved in pain and addiction. These investigators made atomistic comparisons of the structure of the transmembrane domain of known G-protein coupled receptors. They found that the variant shared structural and functionally related characteristics with the native human MOR, including its helical secondary structure and a comparable degree of affinity for naltrexone. Delta opioid receptors (DOR) play an important role in neuroprotection and cardioprotection.[16] Positive regulation of the expression and activation of the receptor increases tolerance to the neural stress mediated by hypoxia/ischaemia.[17,18] Through different mechanisms and levels, DOR activation depends on the duration and severity of stress.[19] This activation serves to foster neuron survival, achieve homeostasis,[17,20] increase survival signalling by proteins that regulate apoptosis (PKC, ERK, Pcl2), and augment the antioxidant capacity of those proteins.[21] This is not the case for neurons in the hippocampus[22] due to low-density distribution of these receptors.[23]

Effects of morphine on neonatal brain plasticity

Early prenatal exposure to morphine results in functional and structural changes in the nervous system.[24–26] When the drug is given to rats in the first 7 days after birth, neuronal apoptosis accelerates in regions involved in sensory processing (the cortex) and emotional memory (amygdala). However, regions involved in learning (hippocampus) and in autonomic and nociceptive processing (hippocampus, hypothalamus, periaqueductal grey matter) do not display changes.[27] Other studies of repeated morphine administration to different areas of the brain have delivered contradictory results with regard to changes in dendritic spine plasticity,[28] or they list different factors as modulators of brain plasticity.[29–31] The brain-derived neurotrophic factor is one of the various elements involved in plasticity in different brain regions, including the hippocampus, the caudate nucleus and putamen, and the NAc. Changes in these regions are associated with the drug-seeking behaviour seen in morphine dependency, for example.[29] As such, glutamate (Glu) homeostasis is a crucial factor in the dynamics of synaptic and extrasynaptic levels of glutamate, and their impact on circuitry in the prefrontal cortex (PFC) and NAc. Increased release of glutamate (Glu) is seen in these regions after repeated drug use.[32] Other studies have reported a significant change in the expression of postsynaptic proteins[33] in association with changes in the density of dendritic spines and filopodia in the frontal cortex and NAc in male mice (*BALB/c*) exposed to morphine over a 2-month period.[34] No apoptosis or alteration in dendritic spine density in pyramidal cells of the fifth cortical layer was observed only in those albino rats exposed to minimal, short-term doses of morphine (1 or 10 mg/kg) during postnatal periods of rapid synaptic growth (P7, P15, P20).[35] Although these data do not offer concrete proof that neuronal apoptosis occurs in children exposed to opioids, they do call for further studies of the signalling pathways involved in treating pain in paediatric patients.[36,37] At present, observations from rodent studies support the neurotoxic effect of prolonged morphine exposure during the period of cerebral growth.

Effects of morphine on adult brain plasticity

Morphine is used for the treatment of pain, especially in patients with advanced cancer and moderate to severe chronic pain. Its availability, pharmacokinetic and pharmacodynamic characteristics, low cost of production, and evident efficacy are factors that contribute to the dependence and tolerance resulting from repeated use. The brain of an addict has undergone changes that cause loss of control over consumption habits even when they are associated with physical and psychosocial consequences. When exposure to morphine occurs in the prenatal period, it can increase the rat's maintenance of context-related fear memory and provoke psychiatric disorders in adulthood due to changes in hippocampal synaptic plasticity.[38] In the cortex and NAc, morphine increases levels of the proteins contributing to apoptosis: caspase-3, Bax, and Bcl-2.[36] It also promotes reorganisation of synaptic connections (structural plasticity) in brain reward circuits (basolateral amygdala, ventral tegmental area, NAc). Morphine also reduces dendritic branching and the density of dendritic spines of pyramidal neurons of the rat visual cortex after long-term morphine exposure.[39] These changes in connectivity also regulate the spatial and temporal dynamics of glutamatergic excitatory transmission, which affects a number of physiological and pathological conditions: learning, memory, neuronal plasticity, emotions, and mediation of addictive behaviour.[40] Although all addictive drugs cause increases in dopamine (DA) in the striatum, the first neuroadaptive changes can be found in 2 DA receptors: D1R and D2R, which are expressed in spiny neurons. DR2 are classed as inhibitors since they limit the release of DA. Furthermore, decreased DR2 levels are caused by a reduction in the pleasurable effects of the drug. Balance between D1R and D2R enables proper function of the DA pathway. D1R activation therefore plays a critical part in physiological modifications to neurons; hyperstimulation, which is induced by

drug consumption, originates the adaptive behaviours that characterise addiction.[41] Both receptors (D1R and D2R) are co-expressed with Glu receptors in dendritic spines. Indirect interactions between both classes of receptor (Glu and DA receptors) form the molecular basis that enables DA to modulate glutamine transmission and control the striatal plasticity and behaviour induced by drug abuse.[42] Evidence shows that reciprocal modulation of both pathways (Glu and DA) can make it more difficult to understand synaptic signalling in the striatal and limbic systems. As such, we recognise the impact of drug-induced signals on both brain plasticity and behaviour, since morphine-related changes in synaptic plasticity (dendrites and dendritic spines) affect areas of the brain contributing to incentive motivation and reward (NAc).[43] The importance of this alteration lies in the fact that most spines receive excitatory information at the site of the postsynaptic density, which includes receptors, signalling channels, and molecules involved in synaptic activity and plasticity. Dendritic spines provide a closed compartment permitting rapid changes in signalling molecules such as calcium, and this lets the body respond efficiently. This being the case, prolonged exposure to drugs, including morphine, alters the dendrites and spines in brain regions associated with incentive motivation, reward, and learning. With drug exposure, structural plasticity suffers long-term changes that remain after withdrawal of the substance. This shows that drug abuse results in persistent reorganisation of synaptic connection patterns in the regions named above.[43]

Conclusions

The central nervous system in general, and the limbic system in particular, become rapidly accustomed to the presence of opiates. Excessive consumption changes synaptic neuroplasticity, especially in the postsynaptic sites; dendritic spines also undergo changes in density. These changes, occurring during development of the limbic system in general and the dopaminergic system in particular, will have a persistent effect on the reorganisation of synaptic connection patterns in areas that regulate incentive motivation, rewards, and learning throughout adult life. For this reason, experiments should be designed to find ways of mitigating the harmful effects of the drug so as to recover synaptic plasticity.

Funding

UNAM-PAPIIT-IN201613 and CONACyT CB/2013/178841.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to thank Dr D. Pless for correcting the abstract.

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