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Morphine induced, behavioural, biochemical and immunological correlations

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Summary. - Tolerance and dependence on morphine appear more or less simultaneously. Evidence has accumulated that addiction leads to depressed immune function and seem to suggest that dependence is under genetic influence. Morphine and related substances of abuse open perspective on ways to investigate the basic mechanisms related to their cellular and systemic effects.

Key words: morphine tolerance, dependence, immune function, genetics.

Riassunto *(Relazioni comportamentali, biochimiche e immunologiche indotte dalla morfina).* - La tolleranza e la dipendenza nei confronti della morfina si manifestano in tempi molto vicini tra loro. Evidenze sperimentali ad oggi accumulate suggeriscono un'azione depressiva sul sistema immunitario esercitata dalla dipendenza la quale risulta geneticamente modulata. Morfina e sostanze d'abuso correalate aprono possibilità di studio sui meccanismi fondamentali dei loro effetti a livello cellulare e sistemico.

Parole chiave: morfina, tolleranza, dipendenza, funzione immunitaria, genetica.

Background

Morphine is a constituent of opium, which has been a medical therapy for longer than 2,000 years, since at least ancient Roman times. Opium is made by extracting a milky juice from the unripe capsule, or seedpod, of the poppy *Papaver somniferum* (grown abundantly in many Middle Eastern countries) and then drying the exudate to form a gum. This gum-the opium-can be eaten as is or added to a beverage.

By the 16th century opium was being carried by traders to Europe and the Orient. At about that time an opium-containing mixture called laudanum became a popular remedy in Europe for virtually all ailments. Later smoking opium and tobacco together became yet another popular way to obtain the drug's benefit.

In the mid 19th century the introduction of the hypodermic needle made it possible to administer large amounts of drugs by injection. The improved technology, which enabled a drug's effect to be felt quickly, led in many regions of the world to the ready prescription of injected morphine for severe pain. At the same time, more and more people began taking morphine for its emotional effects, and the number of addicts rose [1].

This widespread use of morphine for recreational purposes has raised concerns about its immune suppression. Several studies have drawn a parallelism between morphine (opiates) abuse and immune inhibition. This has been linked to the development of addition which is thought to have genetic component. How are these correlated? This review is an attempting to answer the questions by summarizing studies that have been done in animals to understand the behavioural, biochemical and immunological effects of morphine.

Genetic control of morphine preference

Considerable attention has been devoted to the self-administration of pharmacologically active drugs by non-human subjects, with the underlying hope of gaining insight into the complex etiology of human drug addiction. Co-operation between addiction-prone and addiction-resistant animals could facilitate the identification of casual factors in opiate addiction. Many self-administration routes have been used [2-7]. As it has been claimed that the stimuli associated with the effects of morphine administration are probably more important than the drug itself for the active drug-seeking behaviour [8,9], many authors have considered voluntary preference tests by ingestion-intoxicated rats to be preferred when studying drug addiction. One problem has been the lack of suitable choice models. Recently it has been shown that morphine preferance could be enriched by breeding [10]. High morphine preference rats, might be a valuable tool in the search for a neurochemical basis for morphine addiction.

C57BL/6J mice will drink large amounts of, and display a highly positive preference for, morphine sulphate when it is dissolved in an aqueous solution of sodium saccharin. In indentical test situations DBA/2J mice will drink very little of, and display a strong

avoidance towards, the morphine saccharin solution. This clear separation between morphine accepting and morphine-rejecting animals within a single species combined with a quick and simple method of inducing high levels of morphine ingestion could facilitate the discovery of casual factors in opiate addiction [11].

Tolerance and dependence

Because tolerance and dependence on opioids appear more or less simultaneously, it has often been assumed that they constitute different aspects of the same underlying process, the addiction, rather than two separate events. In retrospect, two parallel lines in opioid research can be identified as being caused by this preoccupation with addictive properties, and the study of the processes of analgesia, tolerance, and dependence with the view to find out how the former differs from the latter two [12].

Tolerance, in general sense, could be defined operationally as a state in which a certain dose of a drug give rise to less effect than that normally obtained or in which the dose of a drug has to be increased over the normal level to obtain a certain effect. On a time scale, tolerance is usually distinguished from phenomena that occur within minutes, which are generally termed desensitization, or tachyphylaxis. Tolerance could be brought about in many species, or acquired, reflecting the ability of an individual to adapt. Inborn tolerance to opioids have been observed in at least one species: the Afghan pika, that belongs to the same family as the hare, is extremely tolerant to morphine but shows normal sensitivity to synthetic opioids [13]. Also tolerance could be differentiated into dispositional, in which the amount of drug reaching its site of action is decreased, or functional, when the sensitivity of the target organ(s) to the drug is decreased [14].

Dependence has been sometimes equated with compulsive drug use. The WHO definition is very broad [15]. It puts the stress on psychological effects in humans rather than the adaptational mechanisms and can accommodate many groups of drugs abuse. It is often difficult to assess in subhuman species psychological effects, where operationally defined end points that would be easier to identify are needed. Dependence is sometimes sub-divided into "psychic" and a "physical" part in which psychic dependence is related to mechanism for reward and drug-seeking behaviour, whereas physical dependence is used to describe adaptive state caused by long-term drug exposure, which is revealed first on termination of the exposure as a withdrawal syndrome or abstinence reaction that could be measured in terms of physiological changes.

Although both tolerance and dependence may result from cellular adaptation, they could reflect different underlying mechanisms, and they cannot be simultaneously determined by measuring the effect on an agonist against a background noise of residual drug levels from previous treatment, whereas dependence is determined by withdrawing the drug [16].

Neuroimmunomodulation by morphine and other opiates

Since the earliest documentation of AIDS epidemic, intravenous drug abusers have constituted approximately 17% of AIDS cases in the United States [17]. Also, from 8 to 10% of AIDS cases associated with homosexuality and bisexuality share abuse as a co-factor [17].

From as early as 1907, evidence has accumulated that opiate addiction leads to depressed immune function [18]. In the late 1960s and 1970s, the observations that opiate addicts often suffered from opportunistic infection and cancer [18] were construed as indicating that they were experiencing immunosuppression. Contemporary with these observations Brown *et al.* [19] showed that heroin addicts had depressed lymphocyte mitogenic responsiveness and elevated levels of immunoglobulin production. Opiate addicts have been shown to have depressed levels of total T cells as determined by the ability of T cells to form E-rosettes with sheep erythrocytes and that this could be reversed by naloxone. They conjectured that these effects were mediated through opiate receptors [20]. Experimentation with animal models has also demonstrated the immunoregulation and immunocompromising potential of morphine [21]. In addition, endogenous opioids, enkephalin and endorphin, as well as morphine also affect various aspects of immune function. Much work, however, still remains to be done to characterise fully the role of opioids in immunoregulatory phenomena.

In summary the neuroimmunomodulating effects of morphine and related sustances of abuse open new perspective on ways to investigate the basic mechanisms related to their cellular and systemic effects.

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