Molecular mechanisms and rationale for opioid utilization in chronic pain therapy

P. Romualdi, Pharmacy and Biotechnology University of Bologna, Bologna Italy

Tolerance and physical dependence are two pharmacological phenomena that develop after chronic exposure to opiates. Tolerance is the decrease of the pharmacological effect occurring after repeated administration of opioid receptor agonists, and it causes the need to increase the dose to achieve the same effect. Once doses much higher than starting ones are reached, the body loses its homeostasis and physical dependence takes place; in these conditions, alterations in its equilibrium occur and determine the onset of withdrawal symptoms, after the abrupt discontinuation of the agonist administration.

These two phenomena are therefore related to each other and distinct from the psychic dependence or addiction. It is now believed that neuronal adaptation phenomena to chronic opiates occur, involving a complex series of molecular and cellular events, including receptor desensitization, down-regulation and internalization (Romualdi and Candeletti, 2016).

Opiates produce strong analgesia but their use is limited by an increased paradoxical hypersensitivity, known as opioid-induced hyperalgesia, in some cases associated to tolerance. Cellular and molecular mechanisms underlying these phenomena include genetic differences, variants of mu opioid receptor, neurons and glia factors, LTP, neuronal sensitization, neuroinflammation via microglia and astrocytes involvement and epigenetic mechanisms as well (Roeckel et al, 2016). The psychic dependence is a chronic recurrent disorder characterized by a compulsive behaviour, that is, the loss of control over the search and intake of drugs of abuse, regardless of the damage caused to themselves and to others. The reinforcing effects of all substances of abuse are due to the actions on the mesocorticolimbic system, a circuit consisting of prevailing dopaminergic neurons that mainly project from the ventral tegmental area (VTA) to the shell of the nucleus accumbens (NAc), the amygdala, and the prefrontal cortex (PFC). This circuit also includes glutamatergic projections from the PFC and amygdala to the NAc and GABAergic projections from the NAc to the VTA.

Three types of different factors contribute to the vulnerability to develop addiction: factors related to the substance effects, genetics and environment. Recently, it has been proposed that the development of psychic dependence and the vulnerability to relapse after deprivation are the result of CNS neuroadaptative processes that oppose the action of reinforcement of drugs of abuse. Long-term effectiveness of the stimuli associated with drugs of abuse causing compulsive seeking behaviour, observed in animal models of relapse, is reflected in humans by the continuing responsiveness to conditioned stimuli and research of the drug of abuse. This confirms a significant role of learning and conditioning factors in the continuing abuse potential for addictive drugs.

A therapeutically appropriate use of opiates for the treatment of chronic pain has been hindered to date by the incorrect belief that their use will inevitably lead to the psychic dependence. The

current prevailing hypothesis suggests that the therapeutic use of opiates does not associate conditioning environmental stimuli so important in determining the positive reinforcement leading to the compulsive use. The condition in which the drug is taken, and aboveall the underlying painful pathology, does not provide the substrate and the context in which the patient seeks for the drug; clinical findings in the field of pain confirm that the phenomenon of abuse is observed very rarely (Maremmani et al, 2015). To strengthen this observation, it has been demonstrated that during chronic pain condition a large release of β-endorphin induce desensitization of μ opioid receptors located on dopaminergic neurons projecting to NAc, as well as microglial BDNF-induced effects. Both phenomena cause a strong reduction of DA release-related reward (Niikura et al, 2010; Taylor et al 2015).

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