Naloxone : actions of an antagonist

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Chapter 1

Introduction

1.1 Background

The opioid antagonist naloxone has a special place in pharmacology – it has no intrinsic action of its own, but it is able to save lives in the case of life threatening side-effects caused by other drugs. Naloxone is an antagonist for all opioid receptors, but most specifically for the μ-opioid receptor, which is the receptor through which opioids such as morphine and fentanyl exert their effects. Those effects include first and foremost analgesia, but also nausea and vomiting, sedation and life-threatening respiratory depression. It is in the case of the latter effect that naloxone can be life-saving, as it is able to reverse respiratory depression.

Paradoxically, naloxone, as an antagonist, was a side product of the search for an opioid agonist, one without addictive properties. For many centuries, the addictive properties of opium (and later morphine) were the cause of severe medical and social problems. However, there was (and still is) no alternative to morphine when it comes to analgesia. The solution to this problem was expected to come in the form of a non-addictive opioid agonist and since the start of the twentieth century, scientists have been working to find such a compound. This search has been fruitless with regard to a non-addictive opioid agonist, but has produced several opioid antagonistic drugs.

Minor alterations to a drug's chemical structure can change an agonist into an antagonist. The first opioid antagonist, N-allylnorcodeine was discovered in 1915, by changing a methyl group in the codeine molecule to an allyl group.[1] After this discovery, however, the research in non-addictive opioids lay dormant for a while and it would take until 1944 for a second member of the opioid antagonist class, N-allylnormorphine (or nalorphine), to be characterized. Nalorphine showed antagonism for morphine induced respiratory depression,[2] but was later found to be a μ-opioid receptor agonist as well, with severe dysphoric side-effects (due to its agonism of the κ-opioid receptor).[3] Further experimentation with nalorphine's chemical structure finally yielded N-allylnoroxymorphone, or naloxone, in 1960.[4]

1.2 Respiration

Naloxone is best known for its use in opioid induced respiratory depression and it is therefore that the first part of this thesis is dedicated to its use in respiratory studies. Opioid induced respiratory depression is clinically recognized by an increase in arterial P_{CO_2}.[5] This is caused by a reduction of both tidal volume and respiratory frequency, which is in turn caused by activation of the μ-opioid receptors in the respiratory control centers of the central nervous system.[6] This μ-opioid receptor activation leads to a decreased sensitivity of the chemoreceptors, characterized in a right and downward shift of the $\dot{V}_i$-P_{ET,CO_2}-response curve. In other words, opioids cause the chemoreceptors to be less sensitive to carbon dioxide (CO_2), which is one of their main stimuli. Naloxone

can antagonize this effect through competitive antagonism at the μ-opioid receptor and is thus able to save lives by reversing respiratory depression. It is always important to keep resuscitated patients under surveillance, as naloxone's duration of action is often shorter than that of the opioid. This means that renarcotization can occur easily, especially with longer acting opioids such as morphine, heroin and methadone. The duration of naloxone's reversal is highly dependent on the opioid used, and therefore it is important that we characterize naloxone's behaviour in different opioids.

1.3 Pain and hyperalgesia

Essentially, pain is a physiological signalling system: it alerts the brain that something is wrong in the body and thus urges the body to protect itself from further harm. There is a purely physical component to pain, called nociception. This is the conduction of a signal from a nociceptor (a receptor responsive to painful stimuli) or a damaged nerve in the peripheral nervous system on to the central nervous system.[7] But nociception alone is not pain. Pain also has an emotional component, which consists of our response to a painful stimulus. This response is highly variable and depends on both individual and cultural factors.[8] Analgetic drugs, such as opioids, influence one or both of these components and thus cause us to feel less pain. Opioids are renowned for their analgetic qualities – they still form the gold standard in pain therapy. Less recognized is that they may also increase pain sensitivity.

This so-called 'Opioid induced Hyperalgesia' (OIH) has proven to be a growing problem in pain management and has therefore been the focus of much research over the past decade.[9] OIH can in general be defined as an increased pain response due to the use of opioids.[10] For a long time, OIH has been mistaken for opioid tolerance, as both conditions require higher opioid dosing. But at present the general hypothesis is that OIH may be the result of an central sensitization process.[11] This is probably caused by activation of N-methyl-D-aspartate (NMDA) receptors. Heightened activity of protein kinase C removes the magnesium 'lock' off the NMDA-receptor, thereby activating the receptor. This ultimately leads to a higher pain perception. It has been suggested that μ-opioid receptor activation could activate protein kinase C.[12] If naloxone could prevent this activation, it could perhaps be used in the prevention and treatment of opioid induced hyperalgesia.

1.4 Addiction

Opioid addiction remains a social and medical problem. Initial attempts to manufacture an opioid without addictive properties were in vain. The obvious solution was then to try and block the μ-opioid receptor, using opioid antagonists such as naloxone.[13] This causes acute withdrawal syndrome in opioid dependent patients, which can either be a goal of the therapy (in detoxification settings) or a threatening side-effect

(after an opioid overdose).[14] Due to its short elimination half-life, naloxone is not the first choice in maintenance therapy for opioid dependent patients.[15] It is however most famous for its use in the treatment of opioid overdose. Patients overdosing on heroin have a severe respiratory depression, which often results in a comatose state. In those patients, naloxone can make the difference between life or death.

1.5 Aims

With its antagonism of the μ-opioid receptor, there are several applications of naloxone worth investigating. This thesis is specifically aimed to answer the following questions:

- In chapters 2, 3 and 4, the possibility to reverse opioid-induced respiratory depression with naloxone, is explored and the question whether this differs between different opioids is studied.
- In chapter 5, the question is addressed whether naloxone can be used to abolish opioid induced hyperalgesia.
- Chapter 6 is an elaboration upon the roles naloxone can play in the treatment of opioid addiction.

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