Evaluation of Narcotics

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4th Stage

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Algesia (pain)

- an ill defined as, unpleasant sensation, usually evoked by an external or internal noxious stimuli. Its a warning signal and primarily protective in nature, but causes discomfort. Excessive pain may be unbearable, anxious, causing nausea, sweating, palpitation, rise or decrease B.P.

Analgesics

- drugs that selectively relive pain by acting on CNS or peripheral pain mechanisms, without altering consciousness. They relive pain as a symptom, without affecting its cause. They are used when the noxious stimulus cannot be removed or as adjuvant to more etiological approaches to pain.

Pain Perception

1. Activation of pain receptors (nociceptors) in peripheral tissue (muscle, skin, deep viscera) by a number of chemical mediators (histamine, bradykinin, PG, ATP & lactic acid) that released at the site of tissue damage.
2. Transfer of pain information from nociceptors in the periphery to the spinal cord. Excitatory A.A (glutamate, neurokinins "sub. P & neurokinin A") mediate such synapse connection.
3. Onwards passage of pain information to higher centers.

Analgesic drugs divided into:

- **A.** Narcotic/Opioids/Morphine-like
- **B.** Non-narcotic/NSAIDs/Aspirin-like

Opioid/Morphine-like drugs

- **Full agonist**: (pure agonist) like morphine (μ-, k-, δ-agonist).
- **Partial agonist**: produce agonistic effect but may displaced the full agonist from receptor binding and thus ↓ its effect (like buprenorphine).
- **Mixed agonist**-antagonist: has agonistic effect on one receptor and antagonistic on another (like pentazocine- agonist at k receptor & weak antagonist at μ).
- **Full antagonist**: Pure competitive antagonist (like naloxone).

All opioid receptors are G-protein linked & their activation causes:

1. Inhibition of adenyl cyclase & reduce cAMP level.
2. Opening K+ channels & cause hyperpolarization, (↓ excitation).
3. Block the opening of voltage Ca2+ channels & inhibit glutamate & sub.P release afferent nerve fibers.

Pharmacological actions of Morphine
1- on CNS

1. Analgesia
2. Euphoria (a pleasure sensation & freedom from anxiety)
3. Respiratory depression
4. Cough center depression
5. Nausea & vomiting
6. Pupillary constriction (pin-point pupil)
7. Antidiuretic effect

2- on CVS

- Morphine decrease arterial & venous tone → orthostatic hypotension. This effect is beneficial in decreasing ventricular work, pulmonary congestion & edema. Morphine also cause release of histamine from mast cells when given i.v., so it is not recommended during hemorrhagic shock.

3- On GIT

- ↑ tone & ↓ GIT motility → constipation. ↓gastric emptying so affect absorption of other drugs. ↑ intrabiliary pressure by constricting smooth muscles of gallbladder & contract the sphincter of oddi → increase pain rather than relief it. Meperidine & pentazocin cause less ↑ in biliary pressure are preferred in case of biliary colic.
- GIT effect of morphine is partially antagonized by atropine suggest a central action.

4- On Bronchi

- Bronchospasm due to release of histamine. Pethidine do not cause such effect.

5- On Genetourinary tract

- urinary retension – contraction of ureters & detroser muscle relaxation & ↑ tone of bladder sphenicter. Also cause ↑ ADH release.
- Uterus – prolong labor due to ↓ uterus tone.

6- Immunosuppressant effect

- Long-term use of opioid cause ↑ susceptibility to infection.

Tolerance

- Tolerance represents an increase in the dose needed to produce a given pharmacological effect. The mechanism include contineous presence of morphine at opioid receptors → inhibition of enkephalin production & release thus larger doses of morphine would be required to compensate the steadily decrease in peptide availability. When morphine is abruptly withdrawn insufficient concentration of endogenous peptides may cause abstinence signs.

Dependence

- **Physical dependence**: represent withdrawal "abstinence" syndrome characterized by flu-like "rhinorrhea", lacrimation, chills, piloerection, nausea, vomiting, anxiety, insomnia, muscular ache & sweating. These effects are maximal in about 2 days & disappear in 8-10 days.

  Longer acting μ-receptor agonists (**Methadone**) show less intense abstinence syndrome & is used for treating withdrawal symptoms of addiction (heroin).
- **Psychological dependence**: expressed as strong craving for the drug.

Straub Tail Reaction

- Morphine affect the sensitivity of sensory receptors along afferent fibers at the level of spinal cord by depress the polysynaptic reflexes.
- The mechanism by which morphine depress the polysynaptic spinal reflexes is similar to that by which morphine produce analgesia but require a greater doses.
- An example of the facilitatory effects of morphine on spinal cord is in mice in which morphine causes contraction of sacro-coccygeus dorsalis muscle result in elevation of the tail of animal which hold rigid a cross the back of the animal in an S-shape (So called Straub tail).

Testing analgesic action using hot plate method on mice

- The hot-plate test is performed to **measure response latencies** according to the hot plate method. A hot-plate was maintained at 55.0 ± 0.2° C and the animals were placed into the Perspex cylinder on the heated surface and the time (sec) to discomfort reaction (licking paws or jumping) was recorded as response latency, prior to and after administration of the plan treatment. A latency period of 20 sec was defined as complete analgesia and the measurement was terminated if it exceeded the latency period in order to avoid injury.

Thank You