EFFECTS OF EXOGENOUS PAIN RELIEVING SUBSTANCES ON EXPERIMENTAL RESULTS

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Pain or injury, as inflicted upon an animal in an experimental setting, will disturb its homeostatic balance and change its behaviour and its affective state. These changes may have far reaching consequences upon the outcome of experiments and may require the application of proper analgesia. I will discuss these physiological consequences of injury and the effects of analgesia, while assuming that the investigator is not interested in nociception, pain or pain control in itself, but in other biological questions which apparently cannot be answered with the help of completely intact and undisturbed animals.

Injury will not only activate all peripheral and central sensory systems involved in nociception and pain, but invariably also the sympathetic nervous system and the pituitary adrenal system. In parallel with the intensity of pain the levels of catecholamines, ACTH and adrenocortical hormones increase in an attempt by the animal to re-establish homeostasis. The behavioural consequences of injury may range from a mere reflex response to avoidance, flight or escape responses or aggression. One might describe the underlying affective state of the animal in pain as anxiety, discomfort, fear, anger or suffering.

If one now tries to comprehend the consequences of pain for the outcome of an experiment, it is clear that the activation of the sympathetic nervous system results in increased activity of many functions of the body including blood pressure and blood supply, the rate of cellular metabolism, blood glucose concentration and rate of blood coagulation. Higher levels of adrenocortical hormones markedly influence carbohydrate, protein and fat metabolism throughout the body, in addition to their effects on inflammation and the immune system. Adding the behavioural consequences of pain to this already impressive list, one realizes that experiments in conscious animals, in which pain is a possible factor, are always biased by secondary influences on the parameters to be studied. If, on top of this, one adds the biological variation which exists even in inbred animals to a standardized pain stimulus, the logical conclusion is that blocking the pain of an animal in an experimental situation is a prerequisite for obtaining reliable answers to scientific questions.

The next part of this discussion concerns the side effects of pain relieving procedures as used in experimental animals. We will limit ourselves to pain relief obtained by analgesic drugs, since other methods like electrical analgesia or acupuncture are as yet not generally accepted. Three classes of analgesics are in vogue: major analgesics of the opiate/narcotic type, α-adrenergic-type analgesics and minor analgesics of the non-narcotic salicylic type. Introduction of analgesics in an experiment will also have far-reaching consequences on several body functions outside the sensory pain system.

Most widely used in animal experimentation are the major analgesics. Tens
of thousand of papers have appeared dealing with the pharmacology of these compounds, including a wide range of actions in addition to pain relief. For this presentation we will limit ourselves to some aspects of their action relevant for the discussion. Opioids typically act after binding in the body to more or less well defined receptors. These actions have usually been interpreted with respect to the participation of 3 receptors: mu, kappa and sigma. Each drug may act as an agonist, a partial agonist or an antagonist on these receptors. With respect to side effects the mu receptor is thought to mediate respiratory depression, euphoria and physical dependence; the kappa receptor mediates miosis and sedation and the sigma receptor dysphoria, hallucinations and respiratory and vasomotor stimulation. Although this classification is an oversimplification, it indicates that the range of side effects of an individual opioid analgesic is for a larger part dependent on its receptor binding characteristics. Regional distribution in the central nervous system has been correlated with different effects like antitussive, respiratory depression, nausea, vomiting or disturbed vision, while peripheral receptors throughout the gastrointestinal tract participate in the regulation of gut functions, including motility. Acute or chronic administration of opioid-type analgesics may thus evoke a wide range of side effects which include respiratory depression, cardiovascular effects, sedation, excitation, emesis, constipation, blurred vision, mydriasis, miosis, spasmolysis, vagus stimulation, anorexia, stereotypies, catalepsia, etc. Marked differences exist with respect to side effects of individual opioid drugs. Xylazine is a presynaptic α-adrenergic drug similar to the well known antihypertensive clonidine. Presynaptic α-adrenergic agonists have marked analgesic properties in addition to their cardiovascular effects. Xylazine is used in veterinary practice as an analgesic and since adreno-receptors have wide spread occurrence in the body many side effects are inherent to its use. The most well known side effects are respiratory depression, heart rate and blood pressure decrease, gastric dilatation, paralytic ileus and sometimes CNS-stimulation. Its concomitant sedative and non-addictive properties contribute to its popularity.

The minor or antiphlogistic, antipyretic analgesics usually act locally and in the periphery and do not penetrate the central nervous system to the same extent as the major analgesics. Their use has been limited to situations where mild analgesia is indicated. Since the mechanism of action of these drugs is antagonism of plasminogen or prostaglandins, which are abundantly released at the site of injury, the side effect profile of these drugs is largely limited to functions where these tissue hormones play a role, such as platelet aggregation, mucus secretion, local blood flow regulation, bronchoconstriction and uterine contraction. Minor analgesics in general are less efficient in deep abdominal or central pain, but in sufficiently high doses do limit operative and postoperative pain to the same extent as the major analgesics. Since the side effect profile is a lot more favourable, more research into the efficacy of these drugs in experimental situations seems warranted.

In conclusion, pain has marked consequences for normal body function in animals. Experimental procedures, which cause pain, necessarily leave the investigator with a markedly disturbed animal and a small change for a proper answer to a scientific question. Analgesics take away the pain and its unwanted effects but introduce, albeit known, side effects. In order to make a proper choice for a good analgesic, the investigator should take into account the side effect profile of a particular analgesic. Non-narcotic analgesics deserve more attention in replacing narcotic anal-