An Animal Model of Inflammatory Hyperalgesia During Development - An Approach to Defining Analgesia and Anaesthesia in Laboratory Animals (3-Dec-2002)

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The modeling of pain states and analgesic drug effects regularly involve some measurement of reflex responses (Abram 1997). Reflexes have most often been treated as all-or-nothing phenomenon and traditional analysis of reflex activity focuses heavily on defining threshold stimulus strength. While reflex thresholds are a useful indicator of sensitivity, gauging reflex activity over a range of stimulus strengths provides more accurate information on spinal processing (Andrews 1991).

Traditional measures of anaesthetic drug effect i.e. assessing reflex responses to a defined noxious stimuli (Eger 1965) are also closely akin to reflex threshold measures (Dixon 1970). Clearly, there is a large cross over between aspects of measuring efficacy of anaesthetic and analgesic drugs. This over-lap may be a confounding factor in interpretation of animal studies of analgesic and anaesthetic drugs. The potential confusion between anaesthesia and analgesia is compounded by developmental changes in reflex activity. This is of particular importance in paediatric pain research and clinical practice (Fitzgerald 1988).

Reflex activity can be analysed in greater depth if responses to a range of stimulus strengths are measured (rather than simply measuring a threshold). I describe here a model in which flexor muscle activity in response to graded nociceptive stimulation is analysed quantitatively. EMG analysis of the withdrawal reflex is used to obtain an objective measure of reflex activity. By measuring the threshold, amplitude and duration of the EMG response in flexor muscles to a range of stimulus strengths, a summary measure of reflex sensitivity can be defined and is termed "reflex responsiveness" here (Fitzgerald 2001).

Using this measure, several physiological states can be studied including the naïve -anaesthetised state, inflammatory pain-state and early developmental states. This measure is useful for assessing efficacy of analgesic and anaesthetic agents. Differentiating analgesic and anaesthetic drug actions is possible by carefully defining and differentiating drug actions in naïve and pain states. An anaesthetic drug can be defined as an agent that depresses normal reflex responsiveness. A pure analgesic drug can be defined as a drug that returns reflex responsiveness to normal from its enhanced level in a pain-state, without depressing normal reflex responsiveness.

Using this model the postnatal developmental regulation of spinal nociceptive pathways has been studied and the sensitivity of these pathways to halothane and nitrous oxide has been assessed. Analgesic drugs active at the level of the spinal cord (ketamine and morphine) have also been studied following their administration via the epidural route.

Quantitative measurements of nociceptive flexion reflex activity to graded cutaneous stimulation in rat pups shows that spinal nociceptive processing is developmentally regulated and that the anaesthetic effect of halothane is age dependent whereas that of nitrous oxide is not. Spinal sensitivity to morphine and ketamine is also developmentally regulated. While epidural morphine and ketamine both display analgesic actions at low doses and anaesthetic actions at higher doses, the separation of these actions is greater for ketamine than it is for morphine.

Bibliography
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