—Review—

From Pain Research to Pain Treatment: Role of Human Pain Models

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Abstract

There is no objective measure of pain; we can however measure different aspects of the pain perception. Earlier experimental pain models often only involved induction of cutaneous pain. Recently new experimental models have been developed eliciting deep muscle and visceral pain that may more closely resemble the clinical pain condition. It is imperative to use multi-modal and multi-structure pain induction and assessment techniques, as a simple model cannot describe the very complex and multi-factorial aspects of clinical pain.

The importance of peripheral and central hyperexcitability for acute and chronic pain has been demonstrated in animals and to some extent in humans. But in spite of our immense knowledge we still do not know how to prevent and treat this hyperexcitability. Our understanding of nociceptive mechanisms involved in acute and chronic pain and the effects of anaesthetic drugs or combinations of drugs on these mechanisms in humans may also be expanded with experimental human models. This knowledge can then help us to develop and test therapeutic regimes in patients with acute and chronic pain.

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Key words: experimental pain model, human, pain assessment, pain stimulation, analgesia, drug evaluation

Introduction

Nociception involves multiple steps from the peripheral receptor, the afferent nerve transmitting the impulse to the spinal cord, the signal processing in the dorsal horn, with inhibitory and facilitatory elements and finally transmission to higher cerebral centres where the peripheral nociceptive stimulus is perceived as pain. Development of new analgesic drugs is a long process. Basic physiological research reveals receptors and transmitter substances that may be involved in nociception. These can then be targeted for further research into analgesic drugs that specifically inhibit or reduce the responses revealed by the basic research. At this stage usually only receptors or cellular models are involved. The next step involves spinal cord slices or spinalized animals (usually rats) where the substances can be tested in more complex models where further elements of the nociceptive system can be included. Finally the substances can be tested in intact animals where the total effect of a substance on all the complex interactions of the nociceptive system can be evaluated. If then, after toxicological testing the substance still seems promising, human phase 1 clinical studies may be started. Often clinical studies are initiated directly based on the animal data. However this may be a questionable procedure. Problems may arise when transferring animal results to humans.

Different species may show different reactions,

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receptor populations and the relative contributions of different aspects of the nociceptive system may be different. Secondly the final investigations on the intact animals use experimental pain models. Animal experimental pain models are usually simple models employing either heat or pressure pain, but do experimental pain models reflect the clinical pain? The answer is clearly no! Clinical pain is not a simple entity, but very complex and multi-factorial, and can therefore not be described with one simple model. The aim of this chapter is firstly to supply the clinician with background knowledge on experimental pain models, their advantages but also their limitations. Secondly we want to promote the understanding that human experimental pain models may expand our knowledge in a way which may not be possible with traditional clinical testing.

Basics of experimental pain

The stimulus and the measured response

In experimental pain we need a stimulus that will elicit pain and a measure of the response to the painful stimulus (for further information see[1]). Let us first examine the stimulus.

Ideally an experimental pain stimulus should have the following characteristics[2,3].

- *Non invasive*, and produce no tissue damage
- *Specific* : measure pain and not other sensations
- *Sensitive* : be able to measure pain within a range which is ethically acceptable and physiologically relevant
- *Measurable*, and show a relation between stimulus and pain intensity
- *Variable* from zero to maximal tolerable levels
- *Reproducible*, and frequently *repeatable* with no change in the response over time

Experimental pain stimuli may be electrical, thermal, mechanical, ischemic or chemical. None of these fulfil the requirements for the ideal pain stimulus. Electrical stimulation diffusely stimulates several sensory modalities, heat and ischemia may produce sensitisation of peripheral tissue if frequently repeated. Chemical stimulation can often only be applied once.

The response to a painful stimulus can be assessed by psychophysical, electrophysiological, and imaging techniques. Imaging techniques can be used to investigate the central pain pathway and structures related to pain processing.

Psychophysical assessment

In psychophysical assessments the relation between the intensity of a stimulus and the evoked perception is described. They can roughly be divided in stimulus dependent and response dependent methods (see reviews[2,4]).

In the stimulus dependent method the stimulus intensity is adjusted until a predefined threshold is reached. Three sensory thresholds can be defined :

- Perception threshold—the lowest stimulus intensity perceived.
- Pain detection threshold—the lowest stimulus intensity perceived as painful.
- Pain tolerance threshold—the highest stimulation intensity tolerated.

In the response dependent method series of fixed stimulus intensities are applied. The perceived intensity of each stimulus is then scored. Scoring can be performed using a visual analogue scale (VAS), a verbal descriptor scale (e.g. mild, distressing, horrible, or excruciating), magnitude estimation or cross-modality matching (see review[4]).

Electrophysiological assessment

Electrophysiological assessments have the advantage that they do not rely on a subjective response, and can under certain conditions be employed under general anaesthesia. The response is quantitative, but the main problem is that they may not always be a correlate of pain intensity (se section "interpreting the response"). Two main electrophysiological methods are used: evoked potentials and nociceptive reflexes[5–20].

Temporal and spatial summation (**Fig. 1**)

The evoked responses to a painful stimulus can be highly dependent on the stimulation modality, duration and area stimulated. Applying a nociceptive stimulus to a large area, and thereby stimulating more nociceptive afferents, will elicit a more intense pain then if the same stimulus is applied to a smaller

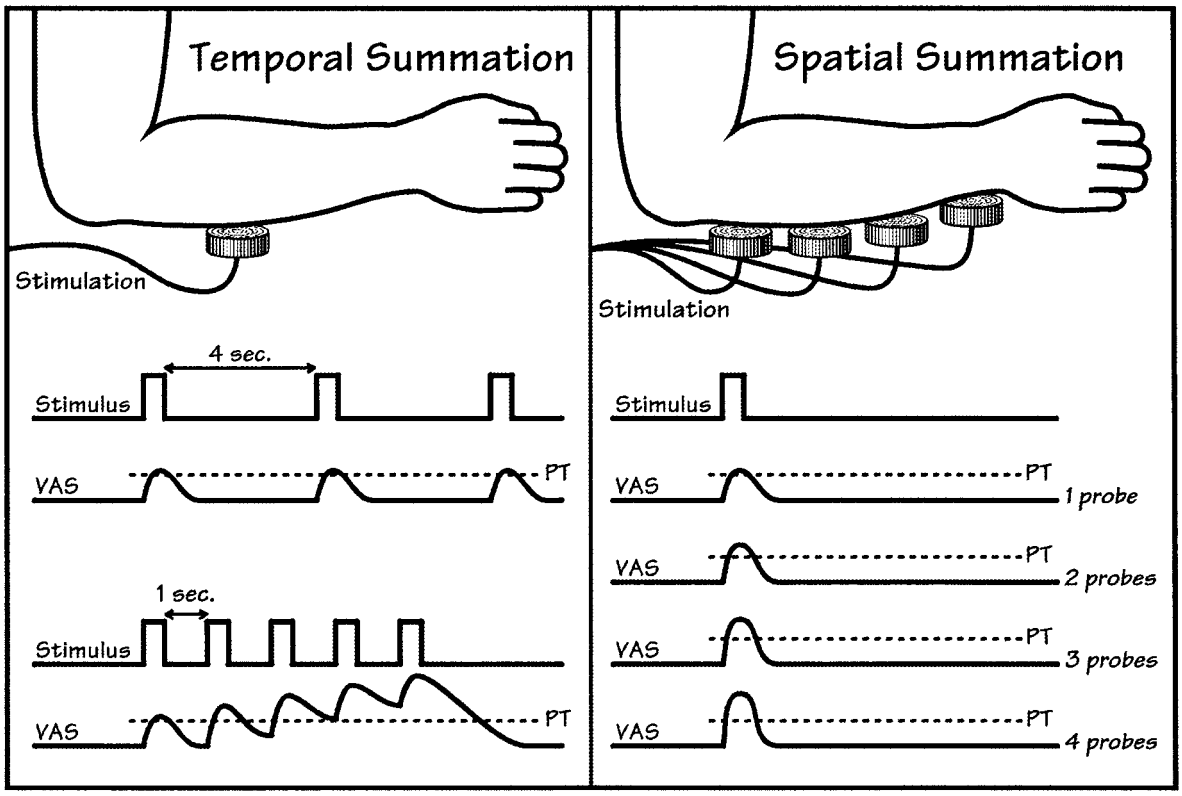

Fig. 1 Temporal summation can be elicited by a series of repeated stimuli. If a stimulus: repeated e.g. once per second the pain evoked (VAS) will increase. Spatial summation is evoked if larger areas are activated. The pain rating (VAS) increase for increased area of stimulation.

area. This phenomenon is termed ***spatial summation***. Spatial summation has been observed within the same dermatome and between dermatomes[21].

Repeating nociceptive stimuli may also cause a central summation of the afferent stimuli[22] and increase the response. This is termed ***temporal summation***. For heat stimuli the repetition frequency has to be above 0.3 Hz[23]. For electrical stimulation the frequency is intensity dependent[24]. Temporal summation can be assessed by psychophysical pain ratings or by increases in the amplitude of the nociceptive reflex elicited by the repeated stimuli.

Short lasting stimuli and stimuli applied to small areas are inhibited to a larger extent by some anaesthetic drugs than long lasting stimuli or stimuli covering larger areas[8,9,12,17,25–28] eliciting temporal or spatial summation mechanism. This demonstrates the importance of temporal or spatial summation mechanisms.

Interpreting the measured response

We cannot directly measure pain, but we can measure different components which together are important for the pain experienced. The perceived pain intensity and quality can be recorded in awake humans, and this is the main advantage with human compared to animal models. In animals invasive techniques, like direct recordings from the spinal cord dorsal horn, can be employed. Such techniques are obviously not possible in humans. In humans we have to rely of indirect measures of nociception. These are however often complex with non-nociceptive elements that may also be influenced by the substance tested.

Let us use an example to illustrate the problems that may arise in interpreting the response. Zbinden and co-workers[29,30] examined the effect of the inhalational anaesthetic isoflurane on two different responses to painful stimuli. They found that isoflurane could suppress the movement response to the painful stimulus, but not the haemodynamic reaction. Isoflurane decreased the initial pre-stimulus blood pressure in a dose related manner, but did not attenuate the post-stimulus increase in blood

pressure. So Zbinden and co-workers applied a painful stimulus, recorded two different responses and thereby obtained two completely different results. Isoflurane could suppress one response, but had no effect on the other response. Which response is then a measure of analgesia? We get further confused if we then add a known analgesic e.g. an opioid. An opioid will reduce the concentration of isoflurane required to suppress a motor response[31,32] and will also reduce the haemodynamic response[33]. But the question remains: Is isoflurane an analgesic? We have no objective measure of pain, or of the activity of the nociceptive system. What the example illustrates is that we have to employ indirect measures in an attempt to quantify the activity of the nociceptive system. But when we use these indirect measures we also measure the effects of isoflurane on the non-nociceptive components of the response. When we use the motor-response to a painful stimulus, isoflurane could have an effect on the nociceptor, the afferent nerve, spinal synapses or interneurones, the efferent motor-fibre or the motor-endplate. So we are not just measuring the effect on nociceptive pathways. However as we pointed out, humans can rate the perceived pain. Let us illustrate the importance of the subjective rating with another example. Arendt-Nielsen[18] showed that the amplitude of the long latency evoked vertex potential to argon laser nociceptive thermal stimulation correlated with the intensity of the perceived pain. With this method an analgesic effect of alfentanil[34] ibuprofen[35], paracetamol[36], codeine[37], and epidural morphine[38] has been demonstrated. The evoked potential would therefore seem to be a good measure for analgesic effects. In a later study we showed that sub-anaesthetic isoflurane concentrations (0.10～0.26 vol% end-tidal) decrease the amplitude of the evoked vertex potentials to painful laser and intracutaneous electrical stimuli[10]. This could be interpreted as an analgesic effect of isoflurane. But isoflurane produces a similar reduction in the amplitude of non-pain related auditory evoked vertex potentials recorded with the same paradigm, and did not reduce the perceived pain. Therefore the amplitude reduction may not reflect an analgesic effect, but could be due to a general non-specific effect of isoflurane on cerebral neuronal activity. This is supported by the effects of the hypnotic propofol and the opioid alfentanil on the evoked potentials to painful and non painful stimuli. Propofol and alfentanil both reduce the amplitude of evoked vertex potentials to painful laser and intracutaneous electrical stimulation, but both also reduced the amplitude of non-pain related auditory evoked potentials[9]. The hypnotic propofol did not change the perceived pain to the painful laser and electrical stimulations, whereas the analgesic alfentanil, as expected reduced the perceived pain.

So in summary the stimulus used should induce a distinct pain, and it should preferably elicit temporal and/or spatial summation mechanism. Subjective pain ratings should be used whenever possible especially when indirect response measures are recorded. If possible, the effect of non-painful stimuli on the indirect measure should also be recorded, in order to control for non-nociceptive effects on the indirect response.

The importance of multi-modal multi-structure stimulation and assessment

When we study pain in humans we are in reality investigating a complex multiple input-multiple output system, because pain is subjective and multidimensional (se review by Arendt-Nielsen[39]). If we just investigate the reaction to a single nociceptive input the results will only represent a very limited fraction of the pain experience. Furthermore anaesthetic and analgesic drugs may have differential effects on the different pathways of the nociceptive system. So only a multi-dimensional sensory testing involving several stimulation modalities and a multi-dimensional assessment technique may allow us to draw comprehensive conclusions. Each added stimulation and assessment modality will increase the amount of information obtained in a study, but this will also increase the difficulties of interpreting the data as we have illustrated above. In many animal and human experimental studies often only one stimulation modality is used and only one assessment technique. The following example illustrates the importance of using multi-modal stimulation and assessment

techniques.

We have shown that sub-anaesthetic concentrations of propofol will increase the threshold of the nociceptive reflex to single stimulations[9]. Comparing this result with earlier studies using a similar stimulation modus (the flexor reflex)[5,40], could let us to conclude that propofol has an analgesic effect. But the threshold of the nociceptive reflex to repeated stimulations (eliciting temporal summation mechanisms) is not effected by propofol[9], indicating that propofol with the repeated stimulations does not have an analgesic effect. However a hyperalgesic effect of propofol is indicated by a reduced pain tolerance to mechanical pressure[9]. So if we had only used one of these stimulation paradigms we could be lead to 3 very different conclusions. One that propofol has an analgesic effect, the second that propofol has no analgesic effect, and the third that propofol induces hyperalgesia!

The opposite effect of isoflurane and ketamine on the nociceptive reflex to single and repeated stimulations is a further example. Isoflurane increases the threshold for the reflex to single stimulations, but not the threshold to repeated stimulations[8]. Ketamine has no effect the threshold for the reflex to single stimulations, but increases the threshold to repeated stimulations[41]. So what do these results indicate? Is isoflurane an analgesic, is ketamine, are both or none of them? If we expand the experimental testing and include further painful stimulation modalities, we can demonstrate that isoflurane has no or at best only a very weak analgesic effect[10,42], and that ketamine has an analgesic effect[17,41]. This also indicates that the repeated stimulations eliciting temporal summation are more "robust" in that they are little influenced by sedation[9].

Recently Curatolo and co-workers showed that the same electrical stimulation produced markedly different results when the stimulation was applied intramuscular compared to transcutaneous[43]. Remifentanil caused a higher increase in the muscular pain thresholds than in the cutaneous pain thresholds. So we now have to include also a multi-structure stimulation and assessment technique.

Human experimental pain and anaesthetic/analgesic drugs

In the clinical situation conditions are not standard because the patients have coexistent diseases, and operations vary in type and extensiveness. The emotional, psychological and cultural factors vary, and a pathological re-organisation of the nociceptive system due to chronic pain may be present. However in the experimental setting controlled conditions can be achieved. The stimulus intensity, duration and modality can be defined and kept constant over time, and the psychophysical and physiological responses can be quantified. Furthermore the patient or volunteer can be used as his/her own control thereby minimising inter individual response variation, and variation over time.

But are experimental data relevant for the clinician? In experimental volunteer studies the psychological/emotional aspects cannot be simulated. Experimental pain usually involves cutaneous stimuli, whereas clinical pain usually involves deep structures and an inflammatory response is present. Recently experimental models have been developed inducing deep pain (intramuscular and visceral pain) and an inflammatory reaction. A main challenge for the future is to develop experimental pain models more closely reflecting clinical pain.

Evaluating anaesthetic and analgesic drugs

We have above stressed the importance of multi-modal and multi-structure stimulation and assessment techniques. No single experimental pain test will be applicable for all classes of drugs. A battery of pain tests covering different pain modalities, pain mechanisms and structures is therefore imperative. This is especially true when new drugs or combinations of drugs are tested. With the different pain modalities and stimulation paradigms an analgesic profile for different classes of drugs may be established. Possible mechanisms of action of the investigated drug may thereby be indicated. The effect of some anaesthetic drugs on cutaneous experimental pain tests are summarised in the following table.

The differential effect of these drugs on different pain modalities is illustrated.

Peripheral and central hyperexcitability play a very important role in acute and chronic pain[44-48]. But in spite of an enormous increase in our knowledge on receptors and mechanisms in nociception, we still do not know how to prevent and treat this hyperexcitability. Should we inhibit sensitisation of the peripheral receptor, block afferent nociceptive input, spinal hyperexcitability, or central modulation? Considering the large number of receptors, pathways and mechanisms involved in nociception, it is unrealistic to believe that a single drug or intervention will be able to block or attenuate all of these processes. Most probably we need to use a combinations of drugs with effects on different mechanisms and receptors—the concept of balanced analgesia[47,49]. But which drugs should we use and what is the optimal combination? Recently Curatolo and co-workers[50] have described a stepwise optimisation procedure for drug combinations. Experimental human pain models will probably play an important role in expanding our understanding on the effects of anaesthetic drugs combinations on nociceptive mechanisms in humans. This knowledge can then help us to develop and test therapeutic regimes in patients with acute and chronic pain.

Regional anaesthetics and analgesics

Sensory assessment of regional analgesia, including experimental pain models, has recently been reviewed by Curatolo and co-workers[51]. In this section we will illustrate with some examples how experimental pain models have expanded our knowledge with clinical impact.

In an early study, Arendt-Nielsen and co-workers[26] showed that the upper level of adequate epidural analgesia using bupivacaine 0.5% was dependent on the stimulation modality. Stimulation with 10 needles and laser stimulation could evoke pain in dermatomes with adequate analgesia to a single needle. Brennum and co-workers in an elegant series of studies[28,52-55] expanded these findings, and showed, that epidural local anaesthetics inhibit stimuli of short duration and covering small areas to a greater extent than stimuli of the same modality which were more prolonged or covered larger areas. This again stressed the importance of using stimuli that elicit temporal and spatial summation mechanism (see previous section on temporal and spatial summation). These studies indicated that our standard clinical testing methods (pinprick and cold) may be insufficient. This was then clearly demonstrated by Curatolo and co-workers[12]. After 20 ml bupivacaine 0.5% nine of ten patients still perceived the temporal summation of a repeated electrical stimulation (increase in pain perception during the repeated stimulation), even though the perception of pinprick or cold could only be perceived in 1 or 2 of the patients. This study and a second study employing the same methodology of temporal summation elicited by repeated electrical stimuli, confirmed the clinical experience that bupivacaine for spinal anaesthesia produces a more "profound" block then epidural bupivacaine[11,12] (**Fig. 2**).

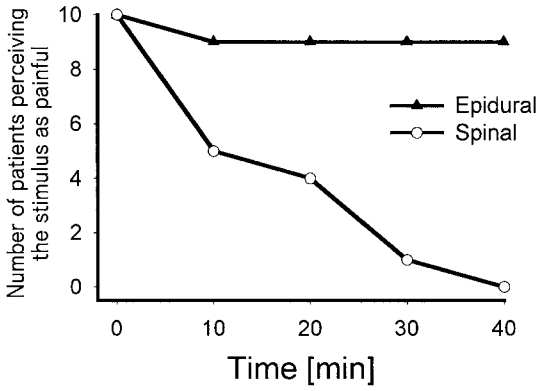

Fig. 2 Epidural and spinal effect of bupivacaine on temporal summation. Only spinal analgesia can block temporal summation.

An old clinical question is whether the addition of CO_2 or bicarbonate can enhance the analgesic effect of epidural lidocaine. With traditional clinical testing methods (pin-prick) Curatolo and co-workers[56] could not establish a difference between plain 2% lidocaine compared to 2% lidocaine with the addition of either CO_2 or bicarbonate. But with the methodology of temporal summation elicited by repeated electrical stimuli, they could demonstrate that pain summation thresholds were higher after lidocaine with bicarbonate compared to plain lidocaine and lidocaine CO_2.This study once again demonstrates

that the results obtained may be very dependent on the stimulus used.

Experimental pain has also been used to demonstrate that epidural fentanyl has a segmental effect (Eichenberger and co-workers, unpublished data, personal communication), whereas epidural morphine spreads to involve also cranial segments[57]. Eichenberger and co-workers in their study further showed that epidural fentanyl may attenuate central hyperexcitability, as temporal summation thresholds were increased by epidural fentanyl. These findings have clinical relevance.

Experimental pain models and chronic pain

One of the important questions in chronic pain is the importance of central hypersensitivity in the determination of the pain complaints. A substantial part of our knowledge on the pathological processes of nociception involved in chronic pain arises from direct spinal cord neurons recordings in animals. In patients, direct spinal cord neurons recordings are not possible. However indirect experimental sensory models may allow us a quantitative estimate of hypersensitivity. Hypersensitivity is assumed when pain is evoked by sensory stimulation that does not induce pain in normal subjects. If pain is also induced after sensory stimulation of healthy tissues at lower stimulation intensities then in normal subjects, its cause must be a hypersensitivity of the central nervous system (central hypersensitivity).

Experimental pain models have been used to demonstrate central hypersensitivity in different chronic pain conditions[58-65]. Koelbaek Johansen and co-workers[59] demonstrated that not only the pain induced by hypertonic intramuscular saline but also the area of referred pain was significantly increased in whiplash patients compared to controls. This was true not only in the neck area but also when hypertonic saline was injected into the anterior tibial muscle, where these patients did not experience spontaneous pain. Similar results were found in fibromyalgia patients by Sorensen and co-workers[61] using intramuscular hypertonic saline and electrical repeated stimuli, and by Curatolo and co-workers[58] in whiplash patients using intramuscular electrical stimulation. These studies show that the processing of nociceptive stimuli is altered in these patients with chronic pain.

Many patients with chronic pain complaints, where even extensive examinations have not revealed a relevant pathology, are often regarded as hypochondriacs. The above referred studies however indicate that central hypersensitivity may be important in several, and possibly in all, chronic pain conditions. If central hypersensitivity is present minor or innocuous stimuli will induce pain, and can thereby contribute to retaining the hypersensitivity state. Maybe even after the initial tissue damage has healed (see also review by Sandkühler[66]). Thereby the discrepancy between pain complaints and the negative pathology that is frequently found in chronic pain patients could be explained. Using experimental sensory models to demonstrate that central hypersensitivity is present in these patients could change future treatment strategies (see also section on research agenda).

Practice Points

- It is essential to use multi-modal, multi-structure pain induction and assessment techniques
- The stimulus should induce a distinct pain and should preferably elicit temporal and/or spatial summation mechanisms
- Subjective pain ratings should be used whenever possible
- When indirect measures are used, a control for non-nociceptive effects should be employed by also testing the effect of non-painful stimuli on the indirect response.

Research Agenda

- New human experimental models involving deep and visceral pain, that more closely reflect clinical pain, are needed
- Further research into the effect of different drug combinations on central hyperexcitability is need

Summary and conclusion

There is no objective measure of pain, and there is no single experimental pain test that will be applicable for all classes of drugs. Multi-modal and multi-structure pain induction and assessment techniques are therefore essential, especially when new drugs or combinations of drugs are tested. An analgesic profile for different classes of drugs, and thereby a possible mechanism of action, can be established by using different pain modalities and stimulation paradigms.

It is important to use stimuli that are longer lasting and cover larger areas instead of brief or very localised stimuli. Thereby temporal and spatial nociceptive mechanisms can be activated. An unspecific effect of time and a sensitisation or de-sensitisation of the stimulated area must be excluded with a placebo control. By simultaneous recording the perceived pain intensity and quality and by also recording the effect of non-painful stimuli on the recorded response, non-specific drug effects on the measured response can be revealed.

The importance of peripheral and central hyperexcitability for acute and chronic pain has been demonstrated in animals and to some extent in humans. But in spite of our immense knowledge we still do not know how to prevent and treat this hyperexcitability. It is increasingly clear that animal data may not always be applicable in humans. Therefore human experimental pain models are essential for validating the animal data in humans. Our understanding of nociceptive mechanisms involved in acute and chronic pain and the effects of anaesthetic drugs or combinations of drugs on these mechanisms in humans may also be expanded with experimental human models. This knowledge can then help us to develop and test therapeutic regimes in patients with acute and chronic pain.

	Electrical stimulation.					
	Single	repeated	heat	cold	pressure	ischemia
isoflurane	++ [8, 42]	0 [8, 42]	0 [42]	0 [42]	0 [42]	?
N_2O	+ [67]	+ [19]	+ [68]	0, + [19, 69, 70]	+ [19]	+ [19]
propofol	++ [9]	0 [9]	0 [71]	(+) [72]	− [9]	?
opioids	+ [6, 7, 9]	+ [9]	0, + [73 — 75]	+ [74, 76, 77]	+ [9, 77]	0, + [78, 79]
ketamine	0 [41]	+ [41]	0, + [17, 41]	?	+ [17, 41]	+ [78, 79]
clonidine	+ [13, 80, 81]	+ [13]	+ [82, 83]	+ [84, 85]	+ [13]	?

+ indicates hypoalgesia, 0 no analgesic effect, − hyperalgesia, ? not known

A summary of how various substances inhibit experimental stimuli.

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