■ REVIEW ARTICLE

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Sensory Assessment of Regional Analgesia in Humans

A Review of Methods and Applications

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SENSORY assessment of regional analgesia is performed routinely for clinical purposes and also plays an important role in anesthesia and pain research. In the past years, new methods were developed and old methods were improved. Technological progress has allowed a more reliable delivery of different stimulation patterns and more advanced recordings of physiologic parameters related to nociceptive processing and modulation. Important developments include methods that explore the activation of different nerve fibers,[1] models that activate specific spinal cord mechanisms (such as temporal summation),[2] and methods that evaluate muscle[3] and visceral[4] pain.

As a result of this new knowledge, the application of sensory testing of regional analgesia in humans must be redetermined. New indications of the use of these methods then can be provided.

In the current article, we update the knowledge available in the field of sensory assessment of regional analgesia in humans. The aims are as follows: (1) to describe and analyze the methods, (2) to define the applications, (3) to provide evidence-based indications for the use of these methods in anesthesia and pain research, and (4) to define areas in which further research is needed.

Methods

Sensory tests are characterized by two aspects: (1) an input, *i.e.*, the stimulus activating the sensory system, and (2) an output, *i.e.*, the measurement of the evoked response[5] (table 1). We first describe the stimulation methods available for activating the sensory system in

regional analgesia. Then, we describe the methods to measure the response, classified as qualitative and quantitative. Finally, we present recent developments in the sensory assessment of regional analgesia.

Methods that are used in regional analgesia or that are of potential interest in this field are reported. A general description of experimental pain models in humans can be found in previous reviews.[5,6] In this article, the term regional "analgesia" is preferred to regional "anesthesia" because analgesia is the common aim of all the regional techniques used.

Stimulation Methods

Mechanical. Sensitivity to touch may be assessed by applying light pressure with a finger[7] or by using a Von Frey hair.[8] Von Frey hairs are calibrated filaments that bend when a certain pressure is reached. Thereby, a slight but exact and reproducible pressure can be applied.[9] $A\beta$ fibers mediate touch sensation.[9]

Pinprick stimulation may be accomplished by gently stimulating the skin with a needle[10] or a safety pin.[11] Pinprick stimulation activates predominantly $A\delta$ fibers.

Pressure pain can be induced by means of pressure algometers.[10] A toe, a finger,[12] or an ear lobe[10] can be pinched between the algometer probe and a pinch handle. The algometer probe can also be applied to a hard body structure, such as the sternum.[10] Both A and C fibers mediate pain induced by pressure stimulation.[13]

Thermal. Cold stimulation may be performed by applying ice,[14] a cold gel bag,[15] a wet alcohol sponge,[7] or a cooling thermode[16] (*i.e.*, a plate whose temperature can be controlled) to the skin. $A\delta$ fibers are assumed to mediate cold sensation in humans.[17,18]

For the ice water test, the hand or the foot is immersed into ice-saturated water (0–2°C) for 1[19,20] or 2[21] min, as long as the subject tolerates the pain. Nociceptors of cutaneous veins appear to mediate cold pain in humans[22] *via* activation of $A\delta$ and C fibers.[23]

Warm sensation can be evoked using the same type of thermode mentioned for cold stimulation[16] because the thermode can cool and heat the skin both. Warm sensation is mediated by C-fiber afferents.[17,18]

Heat pain can be induced by applying the heating thermode to the skin.[24] Heat pain activates $A\delta$- or C nociceptors, depending on whether the skin is heated at

a rapid or a slow rate during threshold determinations, respectively.[25] Warmth receptors are also activated.

Laser pulses evoke a distinct pricking pain.[26] Intensities higher than those evoking pricking pain may cause superficial burns and should be avoided.[26] Pain induced by laser stimulation is thought to be mediated by Aδ and C fibers, depending on the stimulus intensity.[27]

Burn injury is induced to study hyperalgesia. This method is described in the section Recent Developments: Assessment of Hyperalgesia and Allodynia.

Electrical. Electrical stimulation is performed by means of electrodes applied to the skin surface,[15] the intracutaneous tissue,[24] the muscles,[28] or the viscera.[4] Stimulator devices can deliver different stimulation patterns, *e.g.,* different waveforms, frequencies, and duration of the stimulus. Electrical stimulation activates the nerve fibers and, hence, bypasses the receptors. All fiber populations are excited, and the relative proportion of activation of individual fiber types depends on the stimulus intensity.[6] C fibers have a higher activation threshold than do A fibers.[6]

Chemical. Capsaicin is injected intradermally or applied to the skin to induce hyperalgesia and allodynia. This method is described in the section Recent Developments: Assessment of Hyperalgesia and Allodynia.

Mustard oil is applied to the skin to induce inflammation and hyperalgesia. The method is described in the section Recent Developments: Assessment of Hyperalgesia and Allodynia.

Intramuscular injection of bradykinin, serotonin, and substance P produces pain and hyperalgesia.[29,30] These methods are described in the sections Recent Developments: Assessment of Hyperalgesia and Allodynia, and Assessment of Experimentally-Induced Deep Pain.

Intramuscular injection of hypertonic saline induces pain.[3] The method is described in the section Recent Developments: Assessment of Experimentally-Induced Deep Pain.

Ischemic. For the tourniquet test, a pneumatic tourniquet is inflated around the thigh after exsanguination of the leg by gravity.[31] The tourniquet is left inflated for as long as the subject tolerates the pain, for a maximum of 2 h. Pressure at the site of inflation and limb ischemia are responsible for tourniquet pain. Pressure excites A and C fibers.[13] Increase in spontaneous activity and expansion of receptive fields of dorsal horn neurons receiving input from nociceptors proximal to the tourniquet have been described.[32] Tourniquet-induced ischemia causes pain through metabolic and molecular factors that activate C fibers.[33,34]

For the exercise test, the subject performs an activity, such as lifting a 3-kg weight repeatedly[35] or exercising at maximal effort with use of a hand-grip trainer.[36] To enhance ischemia, a pneumatic tourniquet is inflated around the upper arm, either before or immediately after[36] completing the exercise. Exercise induces isch-

emic pain more rapidly than does the aforementioned tourniquet test.

Measurements
Qualitative. Qualitative methods evoke responses that are defined by "categories." Qualitative responses are easy to interpret. For example, the responses "pain" and "no pain" indicate whether the drug or technique used inhibits pain induced by application of a certain stimulus. The main limitation of qualitative measurements is that quantitatively different responses are defined by the same category. Problems related to this feature are presented in the Applications section.

Quantitative. The responses evoked by quantitative methods usually are graded using a continuous numerical scale. The responses elicited by quantitative methods can be measured by psychophysical or electrophysiologic determinations.

Psychophysical determinations are responses to a stimulus, as reported by the subject. The most frequently used parameters for quantifying the analgesic effect are the stimulus intensity to elicit a psychophysical response (threshold determinations), the pain intensity recorded after a standardized painful stimulus is applied (pain rating), and the time during which a standardized painful stimulus is tolerated (duration of tolerance).

For threshold determinations, intensity of the stimulus is gradually increased either continuously or in a stepwise fashion. Drug effect is quantified by recording the stimulus intensity at which the subject begins to perceive the stimulus (stimulus detection threshold), the stimulus intensity at which the stimulus perception becomes painful (pain detection threshold), or the stimulus intensity at which the pain is perceived as intolerable (pain tolerance threshold).[24]

For pain rating, a painful stimulus of a predefined intensity (*e.g.,* 1.5 times the baseline pain detection threshold[24]) is applied. The subject then rates the pain intensity, typically on a 10-cm visual analog scale (VAS), where 0 = no pain and 10 = unbearable pain. Continuous pain rating on the VAS can be used to measure pain during application of a continuous painful stimulus.[3] The area under the curve (*x*-axis = time, *y*-axis = VAS), the peak value of VAS, and the mean VAS are calculated to quantify analgesic effect of a drug.

The duration of pain tolerance is measured by applying a standardized painful stimulus, such as ice-water,[19] electrical stimulation,[31] or a limb tourniquet.[31] The time during which the stimulus is tolerated by the subject is used to quantify analgesia.

Electrophysiologic measurements can be made by recording responses evoked in the peripheral nerves, in the spinal cord, or in the brain. At the periphery, inhibition of nerve conduction after administration of local anesthetics can be measured by use of transcutaneous recordings of compound motor action potentials[11] and

Table 1. Sensory Tests Used in Regional Analgesia

Stimulus Applied	Fiber Activated	Response Recorded
Mechanical		
Touch	Aβ[9]	Intact–abolished perception[7,8]
Pinprick	Aδ[9]	Intact–reduced–abolished perception[7,43,95]
Pressure	A, C[13]	Pain threshold[10]
Thermal		
Cold	Aδ[17,18]	Intact–reduced–abolished perception[7,95]
Ice water	Aδ, C[23]	Duration of tolerance;[19] pain rating[20]
Warm	C[17,18]	Detection threshold[24]
Heat	Aδ, C[25]	Detection threshold, pain threshold[24]
Laser	Aδ, C[27]	Detection threshold, pain threshold, brain potentials;[43,44] pain rating[24]
Burn injury	A, C[68–70]	Hyperalgesia, allodynia[66]
Electrical		
Transcutaneous	A, C[6]	Detection threshold;[14,24,95] pain threshold;[24,91] pain rating;[10,24] duration of tolerance;[31] nociceptive reflex threshold;[10,39] peripheral potentials (peripheral recordings);[11] brain potentials (central recordings)[45,46,92]
Intramuscular*	A[78]	Pain threshold[28]
Visceral*	Aδ, C[81]	Detection threshold, pain threshold[4]
Chemical		
Capsaicin (intradermal)	A, C[73,74]	Hyperalgesia, allodynia[71]
Mustard oil	A, C[75]	Hyperalgesia, allodynia[35]
Bradykinin and serotonin intramuscular*	Aδ, C[76]	Pain rating (area under the curve)[30]
Hypertonic NaCl intramuscular*	C[77]	Pain rating (area under the curve)[3]
Ischemic		
Tourniquet	Aδ, C[13,33,34]	Duration of tolerance[8,31]
Exercise	C[33,34]	Pain rating[35]

* Not yet used for regional analgesia.

sensory nerve action potentials. An electrical stimulus is applied to a peripheral nerve, proximal to the site of injection of the local anesthetic. The amplitude of the aforementioned action potentials, recorded distal to the site of injection, quantifies the drug effect.[11] The main limitation of this method is that action potentials measure the summed activity of all the fibers of a sensory nerve. The recorded potential mostly reflects the activity of large fibers and is less sensitive for detecting the activity of the smaller myelinated and unmyelinated fibers that mediate pain sensation.[11] Therefore, the correlation between depression of the action potentials and inhibition of nociception is not known.

The nociceptive withdrawal reflex is a spinal reflex of the lower limb that is elicited by painful stimulation of a sensory nerve.[37] Transcutaneous electrical painful stim-

ulation of the sural nerve evokes a flexion reflex that can be recorded from the biceps femoris muscle by electromyography.[10] The stimulus threshold to elicit the electromyographic response usually corresponds to the stimulus threshold eliciting a subjective pain perception.[37,38] The stimulus intensity eliciting the withdrawal reflex (reflex threshold) can be used to investigate the analgesic effect of epidurally administered drugs.[10,39] However, supraspinal mechanisms[40] and sedation[41] can affect the reflex threshold. Inhibition of the withdrawal reflex[37] cannot reflect inhibition of nociception after administration of drugs that cause motor block, such as local anesthetics. The threshold to elicit the nociceptive reflex is higher than the threshold to elicit pain sensation after administration of epidural clonidine.[10] Clonidine-induced inhibition of nerve conduction,[42] affecting the motor component of the reflex, may be responsible for the difference between reflex and psychophysical threshold.

Somatosensory evoked potentials are electrophysiologic brain responses to stimuli applied at the periphery. Drug effect on sensory function is quantified by measuring the amplitude and the latency of the evoked potentials after peripheral stimulation.[43–48] However, a reduction in the amplitude of brain evoked potentials after painful and nonpainful stimuli also may be caused by sedation.[41,49] Therefore, depression of evoked potentials does not necessarily imply depression of nociception but may result from nonspecific drug effects on brain potentials or concomitant sedative effects. Epidural clonidine (150 μg) produces marked analgesia in cancer patients but only a minor effect on early somatosensory evoked potentials.[45] Therefore, this method has a low sensitivity for detecting the analgesic effect of epidural clonidine. Several investigations have shown that epidural anesthesia frequently is associated with a small reduction in the amplitude of somatosensory evoked potentials.[46–48] Evoked potentials are the result of a general activation of the sensory system and are not specific correlates of pain perception. It is unclear to what extent they reflect the inhibition of nociceptive transmission caused by regional analgesia.

Electrophysiologic determinations can evaluate the effect of drugs on sensory pathways and mechanisms. However, there are two problems concerning their use in regional analgesia. First, any stimulus applied probably activates nociceptive and nonnociceptive pathways. The electrophysiologic response may be the result of both components. Second, electrophysiologic responses may be affected by drug actions that are independent of the analgesic effect. Therefore, it is often difficult to correlate electrophysiologic measurements with drug-induced antinociception.

Because the subjects usually are awake during regional analgesia, psychophysical responses can be recorded. To date, the subjective report of pain sensation after stim-
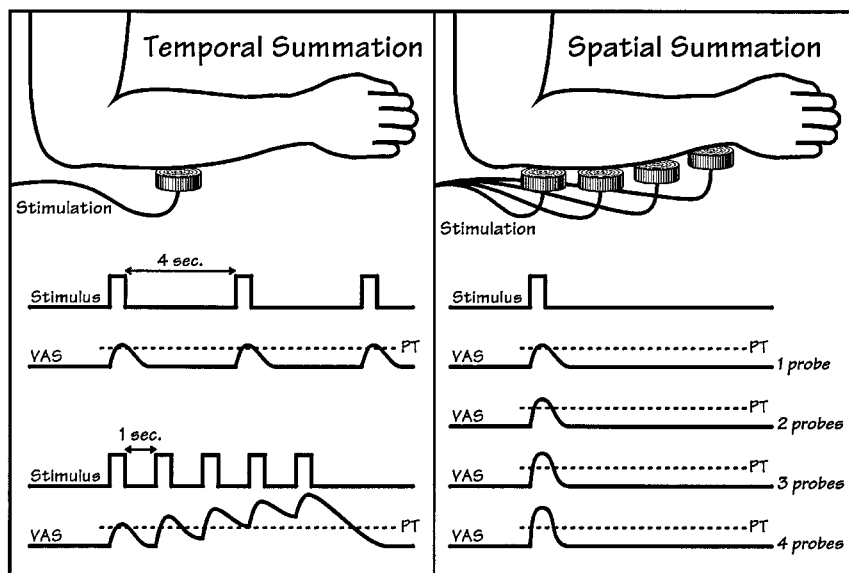
Fig. 1. The figure shows temporal and spatial summation. A heat stimulus (thermofoil thermode), with an intensity producing a subjective sensation at or slightly more than the pain threshold (PT), is used. Temporal summation: If the stimulus is repeated with a low frequency (*e.g.,* every 4 s), the subjective sensation measured using a visual analog scale (VAS) remains the same. If the stimulus is repeated at a faster rate (*e.g.,* every 1 s), VAS score increases during the stimulations because of a central summation of the response. Spatial summation: Increasing the stimulation area, by applying the same stimulus to a larger number of probes, increases the VAS score.

ulation is probably a more reliable correlate of nociception than are available electrophysiologic measurements. Electrophysiologic measurements may provide complementary information. Until electrophysiologic methods more specific for nociception are developed, we rely mainly on psychophysical determinations.

Recent Developments

Assessment of Drug Effects on Different Nerve Fibers. Transcutaneous electrical stimulations at 5, 250, and 2,000 Hz are thought to activate C, Aδ and Aβ fibers, respectively.[14] Therefore, stimulation at different frequencies may be used to study the effect of drugs on nociception mediated by individual fibers. To this purpose, drug effect is analyzed by determining the stimulus detection threshold and the pain threshold at each frequency.[50] However, there is no direct evidence of a selective activation of fibers by the aforementioned frequencies. Electrical stimulation excites nociceptive and nonnociceptive pathways nonspecifically.[6] Because C fibers have a high activation threshold,[6] their excitation after electrical stimulation at 5 Hz is likely to be associated with excitation of the low-threshold Aδ fibers.

Microneurography is the direct recording of the activity of nerve fibers after peripheral stimulation.[51] Needle electrodes are inserted percutaneously in a fascicle of a peripheral nerve (*e.g.,* the peroneal nerve). A stimulus is applied to the corresponding receptive field (*e.g.,* the skin of the foot innervated by the peroneal nerve). Both the electrophysiologic activation of the nerve unit from the needle electrode and the psychophysical response of the awake subject are recorded. This method may identify activation of A and C fiber units and of different classes of nociceptors[52] individually.

Assessment of Temporal and Spatial Summation. Temporal summation is a phenomenon that occurs when repetition of a stimulus increases pain perception

(fig. 1). A single nonpainful stimulus is thus perceived as painful when repeated.[2] Repeated stimulation causes an addition of synaptic potentials in the spinal cord neurons that may ultimately lead to an increased neuronal response.[2] Thus, temporal summation results in a short-lasting spinal cord sensitization. In animal studies, repeated stimulation increases the excitability of spinal cord neurons, which persists after discontinuing the peripheral stimulation.[53,54] This phenomenon is called "wind-up" and is thought to be an important mechanism for the induction and maintenance of acute and chronic pain syndromes in humans.[55,56] Wind-up is mediated by excitatory amino acids *via* the *N*-methyl-D-aspartate (NMDA) receptor.[54] NMDA antagonists strongly decrease pain threshold after repeated nociceptive stimulation that induces temporal summation but have no effect on pain threshold after a single stimulus in humans.[57] Therefore, the NMDA receptor probably is involved in the induction of wind-up and temporal summation.

Temporal summation can be induced by repeated thermal[58] or electrical[2] stimulation of the skin. It has also been elicited by stimulating muscles[3] or viscera[4] in humans. Temporal summation can be measured by either psychophysical (fig. 1) or electrophysiologic responses. In electrophysiologic responses, electromyographic recordings of the nociceptive reflex after repeated stimulation of the sural nerve are performed[2] (see Electrophysiologic Determinations). Five electrical stimuli at a frequency of 2 Hz are applied by means of surface electrodes to the innervation area of the sural nerve. Such a stimulation pattern evokes an increased reflex amplitude during the stimulation, at a current intensity that corresponds to the stimulus intensity causing a subjective increase in the pain perception.[2] This method has been used to measure temporal summation in an

anesthetized subject, from whom psychophysical responses cannot be recorded.[59]

Spatial summation occurs when a nonpainful stimulus is perceived as painful when applied to a wider area[60] (fig. 1). In general, the wider the skin surface on which heat,[61] cold,[62] pressure,[24] or pinprick[26] is applied, the lower the pain threshold. The mechanisms underlying spatial summation are poorly understood. Spatial summation of warm sensation is more easily induced by low temperatures rather than by high temperatures, whereas spatial summation of cold sensation does not depend on the degree of skin cooling.[63] This suggests that different stimulation types may evoke different summation mechanisms. The NMDA-receptor antagonist ketamine inhibits heat pain that arises from a large area more effectively than heat pain that arises from a small area.[61] This suggests that the NMDA receptor may be involved in spatial summation.

Assessment of Hyperalgesia and Allodynia. Hyperalgesia is an increased response to a painful stimulus, usually observed after tissue injury and inflammation. Both a sensitization of nociceptors in the injured tissue and an alteration of the central processing of the sensory input are involved in its pathophysiology.[64] Allodynia is the induction of pain by an innocuous stimulus. Allodynia results from a dysfunction of peripheral nociception and from alterations in the central modulation of the afferent input.[65]

Hyperalgesia and allodynia are present in several acute and chronic pain states and have been studied extensively in animal models. Burn injury, capsaicin, mustard oil, bradykinin, and serotonin can be used to study hyperalgesia in humans. Primary hyperalgesia (*i.e.*, hyperalgesia at the site of injury) can be studied by determining pain thresholds after heat and mechanical stimulation.[35,66] The area of secondary hyperalgesia (*i.e.*, hyperalgesia at tissues outside the injury) can be determined by brush and pinprick stimulation of the skin surrounding the injury.[35,66]

For burn injury, the same type of thermode used for inducing heat pain (see Stimulation Methods) is applied. A constant temperature of 47°C, applied to the skin for 7 min, does not evoke spontaneous pain after discontinuation of the stimulus but produces primary and secondary hyperalgesia.[66,67] Increased sensitivity of A and C fibers[69] is responsible for primary hyperalgesia after burn injury. C-fiber neuropeptides and excitatory amino acids are involved in spinal cord changes that produce secondary hyperalgesia after heat-induced injury.[70]

Intradermal injection of 100 μg capsaicin (10 μl) evokes a short-lasting burning pain at the site of injection, followed by secondary hyperalgesia in the surrounding tissue.[71] Capsaicin, 1%, moisturizing cream, applied topically for 30–60 min, produces primary and secondary hyperalgesia.[72] Pain induced by capsaicin is mediated mostly by C fibers.[73,74] Secondary hyperalgesia

is the result of changes in the central processing of sensory input from myelinated A fibers that normally transmit nonpainful tactile sensations.[74]

A compress soaked with mustard oil is applied to the skin for 4 min. This evokes burning pain followed by an inflammatory reaction at the site of application and secondary hyperalgesia in the surrounding tissue.[35] The burning pain is mediated by C fibers, whereas hyperalgesia to light mechanical stimuli is transmitted by Aβ fibers, which normally encode nonpainful tactile sensations.[75]

Recently, a method for inducing muscular hyperalgesia by injection of bradykinin and serotonin in humans has been developed[30] but not yet used in pharmacologic studies. Intramuscular injection of bradykinin and serotonin activates Aδ and C fibers.[76] Because physiologic pain mediators are used, this model seems to be of potential interest.

Assessment of Experimentally Induced Deep Pain. Traditionally, sensory tests have been applied to the skin. Recently, experimental models that evoke muscle pain have been developed and validated. Muscle pain can be induced by intramuscular injection of hypertonic saline[3] or physiologic pain mediators, such as bradykinin, serotonin, and substance P.[29,30] The evoked pain can be measured by continuous recording of pain rating on the VAS (see Psychophysical Determinations) and by assessing the size of the body area in which the pain is reported. Muscle pain also can be evoked by intramuscular electrical stimulation and measured by recording the pain threshold of the subject to the electrical stimulus.[28] Local pain (*i.e.*, at the site of intramuscular stimulation) and referred pain (*i.e.*, pain referred at an area other than the stimulation site) can be assessed. Pain induced by hypertonic saline is mediated mainly by unmyelinated afferents.[77] As previously mentioned, intramuscular injection of bradykinin and serotonin activates Aδ and C fibers.[76] Intramuscular electrical stimulation excites thick and thin myelinated nerve fibers.[78]

Visceral pain has been induced experimentally in humans by distention of the gastrointestinal tract[79] and electrical stimulation of the mucosa.[4] Aδ and C fibers mediate pain evoked by distension[80] and electrical stimulation[81] of viscera. The use of these methods is limited by their invasive nature. More research is needed to develop models for visceral pain that are more suitable for experimental testing in humans. Methods that induce muscle and visceral pain have not been used in regional analgesia.

Experimental Applications

In this section, the application fields of sensory tests for experimental purposes are presented. Examples from the available literature are provided that may help

in understanding the characteristics of the methods and their proper use. A review of the effects of regional analgesia on sensory function is not an aim of the current article.

Advantages and Disadvantages of Experimental Sensory Tests.

The main advantages of experimental sensory tests in regional analgesia are as follows:

1. The same stimulus can be applied to different dermatomes to quantify the segmental action of a drug. This characteristic is useful in addressing whether the analgesic effect of epidurally administered drugs results from a spinal or a systemic action.[10,19,44,50,82] The influence of patient- and anesthesia-related factors on the spread of epidural[83,84] and spinal[85,86] analgesia can be studied.
2. Application of a standardized stimulus avoids the variability associated with the type of stimulus. In contrast, large variability of the painful stimuli is common in clinical studies.[87-89] The same testing procedure may be repeated in the same individuals in different sessions, each session being characterized by different treatments (crossover design).[31,90] This avoids the variability associated with the individual response to the applied stimulus. These characteristics make experimental sensory tests particularly advantageous for performing dose–response studies[16] and comparing the effects of different drugs[10,11,82] or techniques.[50,71] To these purposes, experimental studies usually necessitate smaller sample sizes than do clinical studies.
3. The same standardized stimulus can be repeated in the same experimental session to assess the time course of the drug action.[43] This usually is more difficult in clinical studies because clinical pain frequently varies progressively.
4. The mechanisms underlying drug action can be elucidated by using tests that evoke specific pain mechanisms[35,67,71,91] or that activate specific nerve fibers[1] (see Investigating Drug Effects on Pain Mechanisms).

The main disadvantage of experimental sensory tests is that the stimulus applied may differ from any nociceptive stimulus producing clinical pain. The correlation between sensory tests and clinical pain is discussed in the section about clinical applications.

Conclusions. The use of sensory tests in humans provides important information that is difficult to obtain with investigations that are conducted in a clinical setting. Experimental studies cannot replace clinical investigations, but rather complement them.

Applications.

Assessing the Analgesic Effect of Drugs. Because local anesthetics act on nerve conduction, their effects

are detected easily by several different types of stimulation (table 2). Local anesthetics attenuate sensation of touch,[8] cold,[24] warmth,[24] and pinprick.[7] They also attenuate pain induced by laser,[43] electrical,[91] and pressure[24] stimulation. Local anesthetics decrease the amplitude of peripherally recorded action potentials[11] and of centrally recorded evoked potentials[92] (see Methods).

However, investigations that applied multimodal testing procedures frequently found that local anesthetics differ in ability to inhibit stimuli of different natures.[8,24,91] One explanation for the differential block of sensory functions is the different susceptibility to local anesthetics of the fibers that mediate these functions. Direct *in vivo* measurement of fiber sensitivity to lidocaine reveals that C fibers are less susceptible to lidocaine than are Aβ and Aδ fibers.[93] This difference in susceptibility does not appear to depend on fiber diameter.[93,94] Differences in the density of sodium and potassium channels could explain the different fiber susceptibility.[94] An additional explanation for the different effect of local anesthetics on different stimulation types is the important role played by central mechanisms, such as temporal[91] and spatial[26] summation, in the processing of sensory input. These aspects are discussed in the section regarding temporal and spatial summation.

The effects of epidural opioids can be detected by different stimulation methods, such as pain induced by pressure, heat, and electrical stimulation[90] (table 2). However, the ability of these tests to detect the analgesic effect of drugs may vary with the stimulation pattern applied or the type of response recorded. When determining the heat pain threshold, low and high rates of increase in skin heating activate C and Aδ fibers, respectively.[25] Opioids preferentially attenuate nociceptive responses produced by C-fiber activation.[25] Therefore, slow rates of increase in skin heating may be more sensitive than high rates for evaluating the antinociceptive effects of opioids. Pain tolerance is more sensitive than pain detection threshold when the effects of epidural morphine are investigated,[90] probably because a larger proportion of C fibers is activated by pain tolerance tests.

Among nonnociceptive stimuli, epidural opioids increase the detection threshold to warmth but have minimal or no effect on detection of cold and electrical stimulation (table 2).

Analgesia after epidural administration of clonidine can be detected by inducing pressure, electrical, or cold pain[10,19] (table 2). However, segmental spread of analgesia after administration of epidural clonidine varies with the type of stimulation applied.[10] After administration of epidural clonidine (8 μg/kg), the perception of pinprick and cold is affected in 40% and 30% of subjects, respectively. This suggests that epidural clonidine may affect nerve conduction in Aδ fibers,[9,17,18] but the pinprick and cold test do not detect the effects of epidural clonidine in most subjects. Analgesia produced by intra-

Table 2. Effects of Analgesics on Sensory Tests

Drug	Sensory Modality Affected	Not or Minimally Affected
Local anesthetics (epidural)	Pinprick (perception yes/no[15,26,91,95]) Pressure (pain threshold;[24] pain rating;[24] detection threshold[24]) Cold (perception yes/no;[15] detection threshold[24,91,95]) Warm (detection threshold[24]) Heat (pain threshold[24]) Laser (pain rating;[24] pain threshold;[26] brain potentials[26]) Electrical (pain threshold;[15,24,91] detection threshold[24,95])	Electrical (perception yes/no;[24] brain potentials[46–48,92])
Local anesthetics (intrathecal)	Pinprick (perception yes/no[7,8,14,43,103]) Cold (perception yes/no[7,8,14,103]) Touch (perception yes/no[7,8,14]) Electrical (pain threshold;[14,103] detection threshold;[14,100] duration of tolerance[8]) Laser (pain threshold;[43] brain potentials[43]) Tourniquet (duration of tolerance[8])	
Local anesthetics (peripheral nerve)	Touch (perception yes/no[11]) Pinprick (perception yes/no[11]) Cold (perception yes/no[11]) Warm (perception yes/no[11]) Electrical (peripheral potentials[11])	
Opioids (epidural)	Pressure (pain threshold[90]) Warm (detection threshold[90]) Heat (pain threshold[90]) Laser (pain threshold;[44] brain potentials[44]) Burn injury (hyperalgesia, allodynia[66]) Electrical (pain rating;[82] pain threshold;[50,90] nociceptive reflex[39])	Pinprick (perception yes/no[82]) Cold (perception yes/no;[82] detection threshold[90]) Electrical (detection threshold[50,90])
Clonidine (epidural)	Pressure (pain threshold[10]) Ice water (pain rating[19]) Electrical (pain threshold;[10] pain rating;[10] nociceptive reflex;[10] brain potentials[45])	Pinprick (perception yes/no[10]) Cold (perception yes/no[10])
Clonidine (intrathecal)	Heat (pain rating[71]) Capsaicin intradermal (hyperalgesia, allodynia[71])	
Epinephrine (epidural)	Pinprick* (perception yes/no[10]) Cold* (perception yes/no[10])	Pressure (pain threshold[10]) Electrical (pain threshold;[10] pain rating;[10] nociceptive reflex[10])
Adenosine (intrathecal)	Exercise (pain rating[35]) Mustard oil (hyperalgesia, allodynia[35])	Touch (detection threshold[35]) Ice water (pain rating[35]) Warm (detection threshold[35])
Neostigmine (intrathecal)	Ice water (pain rating[20])	

For each sensory modality, the type of stimulation and the type of response (the latter in parentheses) are presented.

* Hyposensitivity observed in a subgroup of subjects.

thecal clonidine can be detected by pain evoked by thermal stimulation or application of capsaicin.[71] Segmental hypoalgesia after epidural epinephrine can be detected by pinprick but not by electrical or pressure stimulation.[10]

Intrathecal adenosine attenuates ischemic pain and reduces the area of secondary allodynia after experimentally induced inflammation but does not affect pain induced by cold water[35] (table 2).

The analgesic effect of intrathecal neostigmine can be detected by cold pain[20] (table 2). When added to bupivacaine, intrathecal neostigmine prolongs the duration of tolerance to electrical stimulation and the duration of tolerance to thigh tourniquet.[31]

In conclusion, experimental sensory tests allow quantification of the regional effects of drugs. Drugs used for regional analgesia have different abilities to inhibit different stimuli. Depending on the stimulus applied, a drug can be effective or ineffective or act on different body areas. It follows that the use of a single sensory test mostly is inadequate when the effects of new drugs or techniques are studied. A multimodal testing procedure, including stimuli of different nature to explore different pain mechanisms, increases the likelihood of detecting an effect and may provide useful information about the mechanisms underlying the drug action (see Investigating Drug Effects on Pain Mechanisms).

Experimental assessment of regional analgesia has only been performed by applying stimuli to the skin. The findings obtained with skin stimulation may not apply to deep pain. We therefore encourage the inclusion of muscle pain models in the experimental protocols.

Comparing Drugs and Techniques. Sensory tests have been used to compare the analgesic effectiveness of opioids,[82] α_2 agonists,[10] and local anesthetics.[11,15,92] The tests also have been used to compare regional administration with systemic administration of analgesics.[50,71]

The importance of choosing an appropriate method is evident when analyzing the results of an investigation that focused on the analgesic potency of three epidural lidocaine solutions.[15] Differences in the analgesic potency were detected by repeated electrical stimulation but not by pinprick or cold (fig. 2). This discrepancy results from the inherent limitations of qualitative methods, in which different responses are defined by the same category. For instance, the category "no sensation to pinprick" inevitably includes different degrees of sensory block.[26] Therefore, drugs characterized by a different analgesic effectiveness may produce the same "qualitative" response. Furthermore, the pinprick and cold test produce weak stimuli that are blocked more easily than stronger stimuli (fig. 3).[91] Drugs characterized by different analgesic potencies may block to the same extent the perception of weak stimuli, so that no difference among the drugs is detected.

For the same reasons, the time course of sensory block is less precisely described by qualitative methods than by threshold determinations (fig. 2).[15,95] The same response to pinprick stimulation (*i.e.,* absence of sensation) is obtained at dermatomes displaying different degrees of sensory block, as measured by pain threshold after laser stimulation.[26]

In conclusion, experimental sensory tests are powerful for comparing drugs and techniques. It is essential that methods be quantitative. The tests should produce a stimulus that is sufficiently strong to cover the range of responses evoked by the drugs being investigated.

The equipotency of different drugs or techniques for regional analgesia in humans has not been investigated extensively. Lack of information regarding the dose–response curve reduces the reliability of studies that focus on the relative analgesic potency of two drugs.[96] The epidural/intrathecal potency ratio of most drugs is poorly known. Experimental sensory tests are particularly suitable for addressing these issues.

Combining drugs for regional analgesia is a common practice.[97,98] Few studies have investigated drug interactions using sensory tests in humans.[20,31,99,100] More research is desirable to identify the optimal combinations.

Investigating Drug Effects on Pain Mechanisms. Electrical stimulations at 5, 250, and 2,000 Hz have been used in regional analgesia to study the effects of drugs on different nerve fibers (see Methods). Epidural fentanyl increased the pain threshold to electrical stimulation delivered at 5 Hz but not at 250 or 2000 Hz.[50] This confirms the findings of animal studies that showed that opioids mainly inhibit C-mediated nociception.[25] As

Epidural Lidocaine

Pain Threshold after Electrical Stimulation

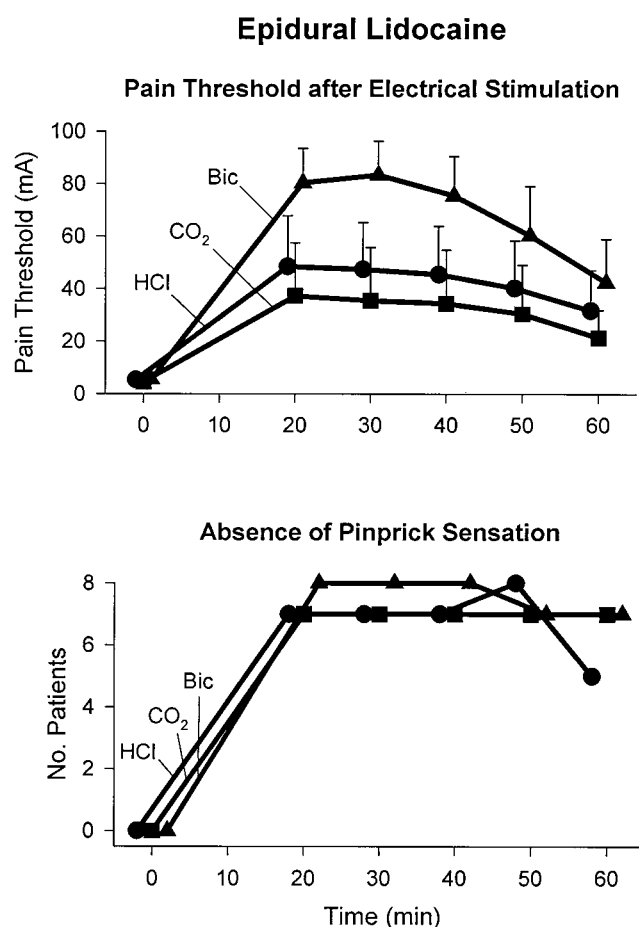**Absence of Pinprick Sensation**

Fig. 2. The graph shows the results of a study that compared three solutions of 20 ml epidural lidocaine, 2%: lidocaine hydrochloride (HCl), lidocaine with carbon dioxide (CO_2), and lidocaine with sodium bicarbonate (Bic).[15] Pain thresholds after repeated electrical stimulation (5 impulses at 2 Hz; *top*) and number of patients in which absence of pinprick sensation was observed (*bottom*) are presented. Both assessments were made at dermatome L4. After analyzing pain threshold after repeated electrical stimulation, block was more intense ($P < 0.0001$) and faster regarding onset (*i.e.,* a steeper slope) ($P = 0.009$) with the bicarbonate solution, compared with the hydrochloride solution. In contrast, no differences in the depth and the onset of sensory block among the three solutions were found using the pinprick test. Reprinted with permission.[15]

mentioned in the Methods section, the results of studies using this methodology should be interpreted with caution, until there is direct evidence for a selective fiber stimulation by different frequencies.

Microneurography (see Methods) has been used to investigate the effect of epidural clonidine,[101] intrathecal morphine, and procaine[102] on efferent sympathetic activity recorded in the peroneal nerve. A comparison of epidural with intramuscular administration of clonidine indicated a probable supraspinally induced inhibition of sympathetic activity.[101] Intraneurally recorded sympathetic activity was not affected by intrathecal morphine but was eliminated by intrathecal procaine.[102]

Repeated electrical stimulation has been used to investigate the effects of epidural and spinal analgesia on

Differential Block
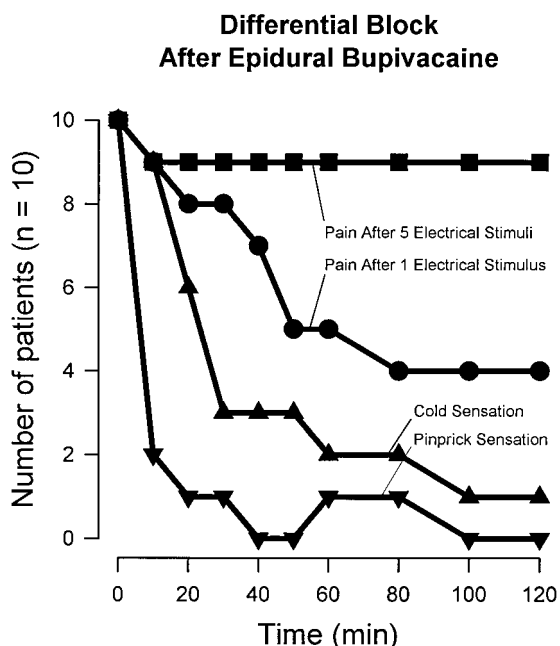## After Epidural Bupivacaine

Fig. 3. The graph shows the results of a study[91] that investigated the effects of 20 ml epidural bupivacaine, 0.5%, on four different stimulations: (1) one single electrical stimulus, (2) five electrical stimuli at the frequency of 2 Hz, (3) cold, and (4) pinprick. Ten patients were studied. Measurements at time 0 represent the basal values. By 120 min, nine patients lost cold sensation and 10 patients lost pinprick sensation. Pain to single electrical stimulation was lost in six patients, and pain to repeated electrical stimulation was lost in one. Reprinted with permission.[91]

temporal summation (fig. 1) in humans.[10,15,91,103] Experimental studies of temporal summation allow inferences regarding the ability of regional analgesia to treat or prevent spinal cord hyperexcitability after repeated stimulation. Epidural local anesthetics more easily inhibit pain induced by short-lasting stimuli than pain evoked by long-lasting or repeated stimuli.[24,91] A single nonpainful stimulus can be perceived as painful when repeated 5 times at a frequency of 2 Hz after epidural administration of 20 ml bupivacaine, 0.5% (fig. 3).[91] Therefore, temporal summation of nociceptive stimulation can be elicited during epidural anesthesia. This is probably because single stimuli, although not perceived as painful, are not blocked completely by epidural local anesthetics and arrive at the spinal cord, where they undergo summation and eventually evoke pain. In contrast, intrathecal administration of 18 mg bupivacaine inhibits pain after single and repeated electrical stimulation, indicating complete inhibition of temporal summation.[103] This may be the result of a strong block of the sensory input, which is therefore unable to undergo summation in the spinal cord to evoke a pain sensation. Because no dose–response study has compared epidural block with intrathecal block, no strong evidence shows that temporal summation is inhibited to a larger extent by intrathecal blockade than by epidural blockade.

Temporal summation is attenuated, but not completely prevented, by epidural clonidine.[10] Epidural morphine

inhibits more easily pain induced by long-lasting stimuli than pain evoked by short-lasting stimuli.[90]

Spatial summation (fig. 1) after epidural[26] and intrathecal[43] administration of bupivacaine, 0.5%, was studied by comparing the response to stimulation using one needle with the response to stimulation using 10 needles applied simultaneously. In both studies, pain was evoked with 10 needles, whereas stimulation with one needle did not evoke pain. Epidural lidocaine, 2%, attenuates more easily the perception of noxious stimuli applied to small areas than it does the perception of noxious stimuli applied to larger areas.[24] Therefore, spatial summation of nociceptive stimulation can occur during regional block. A stimulus applied to a small area, although not evoking a pain sensation, may not be blocked completely and may arrive at the spinal cord. When the same stimulus is applied to a wider area, it can spatially undergo summation in the spinal cord and be perceived as painful.

These data indicate that stimuli of different duration and spatial distribution evoke different pain mechanisms, on which analgesic drugs act in a different manner or to a different extent.

The main implication of these data for clinical practice is that analgesia after a surgical stimulus of short duration or applied to a small area does not guarantee analgesia after a surgical stimulus of long duration or applied to a wide area.

Few trials of regional analgesia in humans include methods for studying hyperalgesia and allodynia. Epidural morphine induced a naloxone-reversible reduction in the area of secondary hyperalgesia after burn injury.[66] Intrathecal clonidine reduced the area of secondary hyperalgesia induced by intradermal capsaicin.[71] Intrathecal adenosine prevented tactile allodynia and reduced the area of secondary allodynia after application of mustard oil to the skin.[35] In contrast, lumbar sympathetic nerve block with use of bupivacaine, 0.5%, did not affect the development of mechanical and thermal hyperalgesia induced by burn injury.[67]

In conclusion, different sensory tests may activate different fiber populations and evoke different pain mechanisms. Therefore, sensory tests can explain mechanisms underlying the pharmacologic action of drugs and investigate specific pain mechanisms in humans.

Because of the importance of summation mechanisms,[104,105] hyperalgesia, and allodynia[106-108] in clinical pain, a greater use of methods that explore these mechanisms is desirable. The inclusion of these models in a multimodal testing procedure greatly enhances the relevance of the investigation. Because microneurography allows for the recording of the activity of different classes of nociceptors and nerve fibers, it is a potentially useful tool for investigating mechanisms underlying the effects of regional analgesia in humans.

Clinical Applications

Predicting the Effectiveness of a Regional Block

In clinical anesthesia, sensory tests frequently are used to assess the spread and the effectiveness of the sensory block in patients before surgery. For this purpose, simple stimuli, such as touch, pinprick, or cold, are applied to the site of surgery. The assumption is that absence of sensation to the applied stimulus predicts absence of pain during surgery, whereas a reduced or normal perception would imply inadequate analgesia. However, block of touch, pinprick, or cold sensation does not imply block of nociception during regional analgesia.[8,87,109–111]

There is evidence of a positive correlation between extent of spread as assessed by sensory tests and effectiveness of regional analgesia. After epidural anesthesia, the larger the number of dermatomes that are hyposensitive to pinprick, the lower the incidence of pain during surgery.[110] Similarly, the intensity of postoperative pain decreases with an increasing number of dermatomes that are hyposensitive to pinprick or cold during continuous epidural administration of a mixture of bupivacaine, fentanyl, and epinephrine.[111] Therefore, the spread of sensory block may be a useful clinical indicator of the effectiveness of the regional block. However, the spread, as assessed by pinprick or cold stimulation, can explain only a limited part of the variability of the effectiveness of epidural analgesia.[110,111] During spinal anesthesia, the spread of block to touch, pinprick, or cold is a poor predictor for pain caused by limb tourniquet or tetanic electrical stimulation.[8] This indicates that adequate analgesia cannot be predicted based only on the determination of the spread of sensory block. Other factors, partly unknown, play an important role.

The most likely explanation for these findings is that touch, pinprick, and cold stimulation differ from the stimulation produced by surgery, and the effect of drugs depends on the stimulus applied. The latter factor is discussed in the section about experimental applications. The differences between sensory tests and clinical pain involve the following factors.

Activation of Different Nociceptors. Tissue damage or inflammation sensitizes nociceptors, which may then respond to nonnociceptive stimulation.[112] In that the nociceptors are not sensitized when the preoperative sensory tests are applied, these sensory tests applied to healthy tissues do not activate the same nociceptors that are involved in clinical pain (*e.g.,* after surgical trauma).

Activation of Different Fibers. Touch stimulation activates Aβ fibers.[9] Therefore, drug-induced inhibition of touch sensation is not a direct indicator of the effect of drugs on the pathways that mediate nociception, *i.e.,* Aδ and C fibers. Cold[17,18] and pinprick[9] stimulation activate Aδ fibers, whereas C fibers are activated by warmth.[17,18] However, these tests may provide only limited information about the drug effects on nociception. Block of pinprick, cold, or warmth sensation does not imply block of all sensory functions that are mediated by the corresponding fibers.[24]

Activation of Different Spinal Cord Mechanisms. Unlike simple sensory tests, noxious stimulation activates spinal cord nociceptive pathways and produces profound central neurobiologic changes.[56] Activation of the NMDA receptor (see Temporal Summation) occurs after only seconds of C-fiber stimulation and is followed after a few hours by gene induction and modifications in the central modulatory system.[113] These changes produce hyperalgesia that may persist when the nociceptive stimulus is removed.[114]

Intensity of the Stimulus. Experimental evidence suggests that regional analgesia blocks perception of weak stimuli more easily than it does perception of strong stimuli. For instance, pain frequently can be evoked by electrical stimulation in the absence of pinprick or cold sensation during epidural anesthesia (fig. 3).[91]

Duration and Spatial Distribution of the Stimulus. Stimuli for sensory tests usually are brief and are applied to small areas, whereas stimuli producing clinical pain frequently are long-lasting and arise from a wide area. Regional analgesia may not block to the same extent stimuli characterized by different duration and spatial distribution (see Experimental Applications).

Site of Application of the Stimulus. Sensory tests used for clinical purposes typically are applied to the skin, and deep nociception is not evaluated. In clinical practice, pain arising from deep tissues is important. Block of cutaneous nociception, as assessed by sensory tests during regional analgesia, is not always associated with block of nociception arising from deep structures, such as postoperative pain evoked by cough or mobilization.[111]

Heterogeneity of the Stimulus. For sensory assessment, a single type of stimulus usually is applied. In clinical conditions, nociceptive stimuli of different intensities and temporal and spatial distribution are applied to tissues characterized by different pain sensitivity.

In conclusion, the simple sensory tests used in clinical practice provide valuable information about the effectiveness of regional analgesia. However, the predictive value of these methods in relation to surgical analgesia is limited. Sensory tests and clinical pain probably activate different pathways and mechanisms.

Sensitivity, specificity, and predictive values of sensory tests in relation to the surgical stimuli have not been investigated. Research in this field would provide information useful for daily clinical practice.

It is possible that the new generation of methods that explore deep pain[3,4] and evoke temporal summation,[2] spatial summation,[60] and hyperalgesia,[30,71] correlate better with clinical pain. Deep pain,[115,116] summation mechanisms,[104,105] and hyperalgesia[106–108] each contrib-

Table 3. Detection of Catheter-related Problems (Epidural or Intrathecal) by Sensory Tests

Analgesia	Response to Sensory Test*	Catheter Position	Management Options
Inadequate	No hyposensitivity at any dermatome	Outside the epidural/intrathecal space[118]	Catheter replacement,[118] change to other anesthesia or analgesia method
		Intravascular†[121]	Catheter withdrawal in 2-cm increments,[118] catheter replacement,[118] change to other anesthesia or analgesia method
	Unilateral hyposensitivity	Far lateral in the epidural space[117]	Catheter withdrawal in 2-cm increments,[118] supplemental systemic analgesics,[97] catheter replacement,[118] change to other anesthesia or analgesia method
	Hyposensitivity not completely covering the site of pain	Possibly too cranial or too caudal[111]	Catheter withdrawal in 2-cm increments (if spread too cranial),[118] supplemental systemic analgesics,[97] use of epidural or intrathecal hydrophilic opioid,[124] catheter replacement,[118] change to other anesthesia or analgesia method
	Hyposensitivity covering the site of pain	Adequate[111]	Additional epidural or intrathecal bolus,[118] increase in infusion rate,[111] change to more concentrated solution,[97] supplemental systemic analgesics,[97] change to other anesthesia or analgesia method
Adequate	Excessive spread of sensory block (after epidural puncture)‡	Possibly in subdural or subarachnoidal space§[122]	Dose reduction,[122] catheter replacement, change to other anesthesia or analgesia method

* After a bolus of local anesthetic. † Detected by test dose with epinephrine.[119,120] ‡ Not explained by high dose (*e.g.*, excessive spread after test dose or sudden increase in spread during continuous infusion at constant rate[123]). § Accidental introduction of the catheter into the subdural/subarachnoidal space[122] or delayed migration of an epidural catheter into the subdural/subarachnoidal space.[123]

ute to clinical pain. The correlation between sensory tests and clinical pain could be improved by combining methods that explore different afferent pathways and different nociceptive mechanisms, thereby rendering the testing procedure closer to the heterogeneous nature of clinical pain. These hypotheses have not been tested and deserve further investigation.

Evaluating the Position of an Epidural or Intrathecal Catheter

Sensory tests are used to evaluate the position of an epidural or an intrathecal catheter. Adequate sensory block and analgesia can be achieved with a broad range of positions of the epidural catheter.[117] However, malposition of the catheter (*e.g.*, dislodgment outside the epidural or intrathecal space,[118] accidental intravascular placement,[119,120] delayed intravascular migration,[121] placement in the far lateral position in the epidural space,[117] position not corresponding to the site of pain,[111] or migration of an epidural catheter into the subarachnoidal or subdural space[122,123]) may result in inadequate analgesia or complications that can be detected by sensory testing. Therefore, sensory tests provide indications about catheter position that contribute to selection of the appropriate treatment (table 3).[97,111,118,124]

After intrathecal[7,43] or epidural[16,24] administration of local anesthetics at doses used for surgical analgesia, hyposensitivity to pinprick and cold stimulation typically is observed in all subjects. Therefore, the pinprick and cold tests used in clinical practice are particularly sensitive for detecting the effects of local anesthetics. Be-

cause opioids and α_2 agonists act mainly on specific pain mechanisms, their effects are not detected by all sensory stimuli. Analgesia after administration of epidural lipophilic opioids[82] and clonidine[10] frequently is associated with a normal sensation of pinprick and cold. Sensory tests capable of detecting the regional effects of opioids and α_2 agonists necessitate the use of sophisticated equipment (see Experimental Applications) and are therefore not suitable for clinical practice. Thus, during administration of these drugs, the position of the catheter usually is evaluated by administering a bolus of a local anesthetic.[118] This is difficult to accomplish at frequent intervals and may cause hypotension or motor block.

In conclusion, sensory assessment of regional analgesia provides clinically useful indications regarding the position of an epidural or an intrathecal catheter. In clinical practice, a reliable sensory assessment of regional analgesia can only be performed when local anesthetics are administered. There is a lack of methods suitable for clinical practice that can be used to assess the regional effects of drugs other than local anesthetics, such as opioids or α_2 agonists.

Because of the importance of opioids and α_2 agonists in pain treatment, the development of sensory tests suitable for clinical practice, capable of detecting the regional effects of these drugs, is desirable.

Conclusions

Research

Sensory tests are useful to quantify the regional effects of drugs, to compare drugs and techniques, to provide

explanation for mechanisms underlying the pharmacologic action of drugs, and to investigate specific pain mechanisms in humans.

The choice of the method adopted may strongly influence the results and conclusions of the investigation. We prefer quantitative determinations to qualitative methods. The range of the stimulus intensity should be enough to include the range of responses evoked by the drug investigated, and multimodal test procedures are preferred to one-test procedures, particularly when new drugs are investigated. We propose an ideal multimodal testing sequence that includes methods that evaluate cutaneous and deep pain, evoke central summation of nociception, and explore clinically relevant pain mechanisms, such as hyperalgesia and inflammation.

Clinical Practice

Sensory tests provide useful information about clinical parameters related to regional analgesia. However, the effectiveness of regional analgesia depends on the intensity and type of the stimulus applied. The stimulation produced by the sensory tests used in clinical practice is different than the stimulation associated with clinical pain. Therefore, the ability of these tests to predict effectiveness of regional analgesia is limited. Further research regarding the use of methods and procedures that more closely mimic clinical pain is desirable. We need methods suitable for clinical practice that can detect the regional analgesic effects of opioids and α_2 agonists.

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