Under normal circumstances most of the visceral input to the central nervous system is not perceived consciously. Visceral hypersensitivity associated with altered reflex activity seems to be a common pathophysiological mechanism in functional gastrointestinal disorders. Investigation of visceral sensitivity in humans is based on distension tests using barostat, or tensostat more recently. Tensostat may allow better standardization of distending stimuli, regardless of the capacity or compliance of the organ being tested. Other techniques include transmucosal electrical nerve stimulation, and chemical or thermal stimulation. Measurement of the responses to gut stimuli is based on the evaluation of conscious perception or objective responses, such as reflex activity or central processes. Recently, the assessment of the central responses has become available due to a variety of new brain imaging techniques. Several factors are thought to influence the results of visceral sensitivity studies: age, gender, physiological factors (postprandial testing) as well as psychological factors (stress, hypnosis, hypervigilance phenomenon). Technical conditions for performing tests like distension protocols may considerably affect the perception of sensory thresholds. Various mediators and pharmacological agents, in particular those acting on serotonin receptors, affect the sensory function of the gastrointestinal tract, and some of them have therapeutic potential in the treatment of visceral hypersensitivity.

**Key words:** visceral sensitivity, stimulation techniques, perception, reflex activity, central responses

**INTRODUCTION**

In healthy humans physiological stimuli to the gastrointestinal tract are rarely perceived. The examples of conscious perception of abdominal sensation include satiety and fullness after a copious meal, inappropriate gas pooling and focal gut distension, or urge to defecate. In patients with functional gastrointestinal
disorders, however, visceral hypersensitivity is commonly observed and regarded as a crucial pathophysiological factor (1).

As with somatic sensation, gut afferent signals reach conscious perception through a three-neuron chain (2). The first order neurons in the dorsal root ganglion arise from the viscera and terminate in the spinal cord. Leaving the viscera the first-order neurons pass through the adjacent autonomic nerve plexus. Second-order neurons project from the dorsal horn of the spinal cord to the brain stem, mainly via the spinothalamic and spinoreticular tracts. Somatic and visceral afferents converging on dorsal horn neurons result in viscero-somatic projection or referred pain. Third-order neurons travel from the brain stem, and terminate largely in the limbic system and frontal cortex. At the level of the gastrointestinal tract sensory neurons of the enteric nervous system and enteroendocrine cells serve as transducers for local reflexes or initiation of afferent projection to the central nervous system (2 - 4).

Various kinds of gut receptors were distinguished including mechano-, chemo- and thermoreceptors, or nociceptors consisting of nonmyelinated C fibers, and fine-myelinated Aδ fibers. However, recently most evidence points toward polymodality of the visceral receptors (5).

Disturbances at every level of the brain-gut axis can affect perception and response to visceral stimuli. Visceral hypersensitivity may arise from gut dysfunction connected with altered receptor sensitivity or chronic disorders of serotonin and substance P production; sensitization of peripheral afferent nerve fibers; spinal hyperalgesia; or distorted processing of gut signals in the brain (1, 3, 4, 6). Some data indicate that the sensory dysfunction in patients with functional gastrointestinal disorders is associated with altered reflex activity, and both mechanisms may interact to produce the symptoms (1).

Although over the last two decades studies on visceral sensitivity in humans have been the subject of considerable clinical research the optimal methods for its assessment are still not well established. Some methods have been partially adapted from somatic sensation studies, just as the terms like hypersensitivity, hyperalgesia, allodynia (Table 1). Different types of stimulation techniques or their combinations are used. In animal models visceral sensitivity may be investigated by applying mechanical, chemical, thermal, electrical, or ischemic stimuli to viscera or visceral

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>hypersensitivity</td>
<td>increased sensation in response to standard stimuli</td>
</tr>
<tr>
<td>hyperalgesia</td>
<td>increased pain sensation in response to some stimuli</td>
</tr>
<tr>
<td>allodynia</td>
<td>appreciation that a stimulus which was previously not perceived as being painful becomes painful</td>
</tr>
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</table>
nervous fibers (7). In human studies physiological, as well as psychological and ethical aspects must be regarded. Influence of local and extraintestinal modulating factors (neural, hormonal, and pharmacological) on visceral sensitivity are also intensively investigated. Gastrointestinal stimulations induce conscious perception, reflex responses, and central responses, and each of these may be evaluated.

**STIMULATION TECHNIQUES**

*Gastrointestinal distension*

Gastrointestinal distension is the most common mode of stimulation. Distension may be performed by manual inflation using a syringe, or with more sophisticated methods such as barostat, and more recently tensostat (*Table 2*) (8 - 10).

*Barostat.*

The principle of the barostat, which consists of a pressure transducer connected by an electronical relay to an air pump, is to maintain constant pressure

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**Table 2. Methods of visceral sensitivity testing**

<table>
<thead>
<tr>
<th>STIMULATION</th>
<th>MEASUREMENT OF THE RESPONSES</th>
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<tr>
<td><strong>Gastrointestinal distension</strong></td>
<td><strong>Subjective response</strong></td>
</tr>
<tr>
<td>barostat, tensostat,</td>
<td><strong>Objective responses</strong></td>
</tr>
<tr>
<td>water/nutrient drink test, gas challenge test</td>
<td>Reflex responses</td>
</tr>
<tr>
<td><em>Chemical, thermal, electrical stimuli</em></td>
<td>Excitatatory and inhibitory gastrointestinal and intestino-intestinal reflexes</td>
</tr>
<tr>
<td><em>Combined stimuli (multimodal stimulation)</em></td>
<td>Interactions between visceral and somatic reflexes</td>
</tr>
</tbody>
</table>

**Subjective response**

- Conscious perception
  - intensity (scores and scale), quality, location, duration,
  - affectivity (e.g., unpleasantness), thresholds

**Objective responses**

- Reflex responses
  - Measurement of cerebral blood flow – fMRI, PET, SPECT
  - Cortical evoked potentials – EEG, MEG
within an intraluminal bag or balloon by injecting or withdrawing the air through a double-lumen catheter. Using the barostat at a constant, physiological level (1 to 2 mmHg above intra-abdominal pressure) changes in intrabag volume reflect variation in the gut tone. Polyethylene oversized bag instead of a latex balloon has been recommended, as the first one has negligible intrinsic pressure and, therefore, does not modify the pressure-volume relationship (compliance) (8, 9). The barostat provides information on gut tone, compliance, and sensitivity during distension. It can be also applied to measure the perception thresholds or physiologic reflexes induced by thermal stimuli, intestinal nutrients or pharmacological agents.

**Distension Protocols**

Technical parameters, such as the pattern and the rate of distension may considerably influence the results of visceral perception studies (8, 9, 11, 12). Two main protocols may be distinguished - phasic distension (i.e., periods of bags inflation separated by periods of bag deflation), or cumulative distension (progressive - ramp or stepwise inflation). Sensory thresholds are higher for rapid inflation than for slow inflation (13). In normal subjects, discomfort threshold are higher during phasic distension than during slow-ramp distension (12, 13). In patients with irritable bowel syndrome (IBS) abnormal sensory responses were reported during rapid phasic distension but not during slow-ramp distension (13). According to these observations it was suggested that different patterns of inflation may preferentially activate different sets of mechanoreceptors and afferent pathways (14). Superficial mucosal and deeper musculoserosal mechanoreceptors seem to be preferentially activated by slow-ramp and rapid phasic rectal distensions, respectively (12, 13).

For measuring the threshold for urgency, discomfort, or pain the ascending methods of limits (ramp, stepwise or phasic) is frequently performed, but it is connected with the problem of the response bias, because sensory reports may be influenced by the past experiences of the subject and psychological factors such as the fear of pain (stimuli are predictable). To minimize response bias random sequence, double random staircase or tracking techniques have been developed (9). Although multiple distensions at each pressure or volume step seem to enable more reliable estimation of sensory thresholds, practical aspects limit the number of trials that can be presented (8). Moreover, the results of some studies have revealed that the simple ascending method of limits are equivalent to the more complicated random staircase method to determine sensory thresholds (15). Generally there are insufficient data to recommend one of these approaches over another (9, 16).

**Tensostat**

Thorough studies on gut sensitivity have shown that neither intraluminal pressure nor volume during distension is the factor that determines conscious
perception (17). Analyzing stretch versus tension modulation it has been claimed that the mechanoreceptors are either in-series (tension mechanoreceptors) or in-parallel (elongation mechanoreceptors) with the muscle fibers of visceral organs (2). In-parallel mechanoreceptors respond to stimuli that elongate the viscus wall, in-series mechanoreceptors respond to stimuli that increase the tension within the viscus wall. It has been suggested that perception of gastrointestinal distension relies on stimulation of tension and not elongation receptors (10, 17, 18). Hence it was proposed that tension rather than pressure- or volume-based distension would be more relevant to the investigation of visceral sensory function (19, 20). The Barcelona group (10) presented a computerized tensostat being somewhat similar to a tensiometer/tensiostat developed by Gregersen and co-workers (21). The tensostat is a computerized pump that can be programmed to apply a fixed tension level on the gastric or bowel wall. The tension can be calculated by using the simplified Laplace law: \( T = \frac{P \times R}{2} \) for a sphere, and \( T = P \times R \) for a cylinder (where \( T \) = wall tension, \( P \) = pressure, and \( R \) = radius, which is determined by volume). However this formula needs a number of assumptions, which are not necessarily fulfilled by the experimental conditions (21). The major assumptions are: (i) the intraluminal balloon and viscus have a perfectly defined (for example, spherical) shape; (ii) the wall of viscus is very thin with constant wall tension everywhere; (iii) the wall of viscus is in static force equilibrium, i.e. the inertial forces are zero, with no contractions; (iv) the pressure external to the viscus is known and is uniformly distributed. All these factors under physiological conditions should be considered, and further validation of tensostat technique is needed.

Water/nutrient Drink Test

In recent years, a liquid nutrient or non-nutrient load test was designed as a noninvasive alternative to sensory studies performed with an intragastric barostat (20, 22 - 24). Subjects ingest water or nutrient liquid at a defined rate (e.g., 15 ml per min) and the maximal tolerated volume is recorded. In some test, the symptoms 30 min after ingestion are measured using visual analog scales. Main advantages of the test are its simplicity, low costs, and quite good reproducibility. Hence, it could lend itself to widespread clinical application, particularly that drinking capacity has been suggested to be impaired in dysmolity-like dyspeptic patients (22, 23), and that the test correlates relatively well with a symptom index or data from barostat-based sensation studies (24). However, discrimination between disease and normal conditions is limited, as almost 50% of dyspeptic patients have maximal tolerated volumes that are similar to those of normal subjects, and the test is not yet standardized across centers (23). Moreover, early satiety or reduced tolerated volume may reflect either hypersensitivity of the stomach or impaired accommodation, which cannot be specifically assessed by this test (20). Further researches are needed to elucidate the accuracy and clinical
applicability of these drink tests and their combination with other tests providing a measurement of gastric accommodation, such as single photon emission computerized tomography (SPECT) or magnetic resonance imaging (MRI).

Gas Challenge Test

Gas challenge test is a novel method for studying gas intestinal dynamics that provides an integrated evaluation of the sensory and reflex responses to intraluminal gas loads (25). The further method - “gas plus lipids” challenge test, can be an example of the combined stimuli, as gas infusion into the jejunum is performed with simultaneous duodenal perfusion of lipids (26). Impaired intestinal propulsion of the gas leading to retention and gut distension, and gut hypersensitivity with poor gas tolerance, or both mechanisms, probably enhanced by intestinal lipids, have been suggested to participate in generation of gas symptoms in IBS patients (27).

OTHER STIMULI

Chemical Stimuli

Bernstein and Baker introduced the acid perfusion test over 40 years ago (28). Originally, the test was intended to reproduce esophageal pain and to differentiate it from cardiac angina. Then it was used to diagnose heartburn. Although the test appears to be highly specific, its sensitivity is relatively low, and a negative result does not exclude an esophageal origin of the chest pain (8). Esophageal hypersensitivity to acid has been demonstrated in non-erosive reflux disease (29), while duodenal hypersensitivity to acid perfusion has been suggested in functional dyspepsia (30). Other chemical stimuli, such as intraluminal fat, do not always induce a significant degree of perception by themselves, but they are able to alter the thresholds for perception to other stimuli, in particular distending stimuli. Physiological amounts of lipids heighten intestinal sensitivity (like in “gas plus lipid” challenge test) by modulating intestinal mechanoreceptor response (31). It is important from the practical point of view, as postprandial perception of gastrointestinal events may be different to that observed in fasted state. Regarding other chemical stimuli, it has been also shown that intrarectal injection of an irritant laxative, glycerol induces hypersensitivity to rectal distension in healthy subjects (32).

Thermal Stimuli

Thermal stimulation, involving both cold and warm stimuli, may be applicable in the gut using intraluminal water filled bags (33). A special temperature probe allowing online recording of the temperature inside the bag providing fully controllable study is recommended (34). Villanova et al. (33) have found that both warm and cold stimulation of the stomach and small intestine (within the
range 12-52 °C) induce specific sensory and reflex responses. Cold stimuli induced abdominal cold sensation and a reflex contraction of the stomach, whereas warm stimuli induced warm sensation and a reflex gastric relaxation. But only warm stimuli in the duodenum induced enterogastric reflexes. Hence, it was suggested that perception and reflex responses to thermal stimuli are induced independently, and conceivably different pathways are involved in these responses (33).

Rectal heat stimulation is another example of a simple technique that has a high degree of reproducibility and may be useful in assessment of polymodal nociceptor function in the rectum (35).

**Electrical Stimuli**

By analog to transcutaneous electrical nerve stimulation, transmucosal electrical nerve stimulation can be applied to the gastrointestinal tract using intraluminal electrodes mounted over a tube (11, 36). Although electrical gut stimulation is not natural and induces non-specific activation of afferent pathways, various models using repeated and continuous burst stimulation provide possibilities of studying visceral sensitivity, central summation, and referred pain phenomena (37). In IBS patients electrical stimulation of the gut elicits less conscious hypersensitivity than produced by mechanical distension, however the areas of abdominal referral of discomfort are similar (36).

**MULTIMODAL VISCERAL PAIN ASSESSMENT MODEL**

Recently, for a first time, a new multimodal model of visceral pain assessment in the esophagus integrating electrical, mechanical, and thermal stimuli into the same device has been developed (34). A probe designed for multimodal stimulation included electrodes for electrical stimuli, and a bag containing a four-electrode impedance planimetry system for mechanical stimuli. Cold and warm stimuli were performed by recirculating water of different temperatures (5-50°C) infused into the same bag as used for mechanical stimuli. The system allowed sequential activation of the individual stimuli with control of site, duration, electrical current intensity, mechanical forces, motility, and temperature inside the bag, hence fulfilling the demands for a comprehensive experimental pain model. The stimuli activate superficial and deeper layers of the gut and therefore resemble the polysensorial experiences present in painful visceral diseases. Multimodal sensory assessment has already been shown to be valid for testing somatic pain, where, e.g., single-modality models have been inadequate for clinical assessment or for pharmacological testing.

**MEASUREMENT OF THE RESPONSES**

Measurement of the responses to gut stimuli is based on the evaluation of conscious perception or objective responses, such as reflex activity or central
processes. Distending stimuli in particular may also be used to measure gut compliance, that is the local response to the distension (11).

**Measurement of Conscious Perception**

Basically, a distinction should be made between the ability to detect intraluminal stimuli and the behavior of reporting the sensation. For example the ability to detect distension, or to discriminate between two distensions, is called perceptual sensitivity. Reporting behavior (i.e., how intense the sensation must be before it is labeled painful) can be influenced by the response bias (9).

Pain or other sensations should be reported on a graduated scale, not in “yes-no” statement. Visual analog scales in which subjects place a mark on a straight line without divisions but clearly delineated end points (e.g., “no pain” vs. “worst pain imaginable”), or verbal descriptor scales, containing 5 to 7 steps, are also recommended. Moreover, it was suggested that the subject should be asked to rate unpleasantness of distension separately from its intensity (9). The use of questionnaires allows evaluation of other than intensity characteristics, such as the type and location of the sensation. For example enlarged and aberrant viscerosomatic referral of intestinal sensation is highly prevalent in functional bowels disorders (13). Other methods include paradigms for thresholds detection. During rectal distension it is usually the thresholds for first sensation, urgency, and pain (11).

**Gut Compliance**

Compliance is the capacity of a hollow organ to adapt to the imposed distension. It is defined as the pressure-volume relationship. Compliance reflects both the capacity and distensibility of the organ (elastic properties of the gut wall), which are modified by many factors including the tone of the organ, local reflexes, contractile activity, and surrounding anatomy. Assessment of compliance is important while the sensitivity of the organ is compared in different conditions (e.g., in fasted or postprandial state or pharmacological studies) (8).

**Impedance Planimetry**

Recently, Gregersen (38) emphasized that true changes in tone in tubular organs must be evaluated in terms of changes in length of the circumference or cross-sectional area, and that tone in spherical organs must be evaluated in terms of changes in the surface area. In most barostat studies focusing on tone, volume rather than circumferential length and surface area are measured. Measurement of volume changes will therefore give at best an approximation of changes in tone (38). Thus recently, a four-electrode impedance planimetry - an alternative method to measure the cross-sectional diameter and wall tension of a tubular hollow viscus, such as esophagus, duodenum, rectum, has been developed (39, 40). Incorporation of a distension balloon in the device facilitates measurement of
the sensory thresholds, while carefully monitoring the physical properties of the
gut wall (11, 34). Two detection electrodes are located inside a cylindrical bag
inflated with electrically conducting fluid. Two outer ring electrodes for
excitation are placed on the probe with a proper distance. Contractions cause
reduction of luminal cross-sectional diameter, while the process of flow over the
sensors results in increase in diameter. The cross-sectional area of the bag is
measured from the impedance of the fluid inside the bag (34).

Measurement of Reflex Responses

Gut stimuli inducing perception elicit also reflexes responses that may be
evaluated by measuring changes in gut tone using barostat. Important
gastrointestinal and intestino-intestinal reflexes include ascending inhibitory
reflexes (the rectocolonic and colonogastric inhibitory reflexes), and descending
excitatory reflexes (the gastrocolonic and ileocolonic reflexes) (11). The barostat
can also record somatovisceral reflexes, such as the gastric relaxation induced by
the cold pressure test, that is, hand immersion into iced water (41). It has been
also shown that a somatic nociceptive cutaneo-muscular flexion reflex (RIII
reflex) can be inhibited by visceral sensation reaching the pain level (14). Thus,
inhibition of this reflex could be used as a new reflexologic technique for
objective evaluation of visceral sensation and somatovisceral interaction.

Studies of the relation between perception and visceral reflexes induced by
intraluminal stimuli have shown that both responses may be mediated by
different neutral pathways and can be independently stimulated. For instance, in
patients with functional dyspepsia (who have selective gastric hypersensitivity),
gastric relaxation in response to duodenal distension was impaired, even though
duodenal sensitivity and compliance was normal (42). Altered reflex activity,
besides sensory dysfunction, seems to be a common pathophysiological
mechanism in functional gastrointestinal disorders.

Measurement of Central Responses: Brain Imaging Techniques

With rapid progress in neuroscience, brain imaging techniques have become
available allowing objective assessment of sensorimotor pathways between the
brain and the periphery, including the brain-gut axis. Gut to brain pathways have
been studied using: functional magnetic resonance imaging (fMRI), positron
emission tomography (PET), single photon emission computerized tomography
(SPECT), cortical evoked potentials (CEPs), and magnetoencephalography
(MEG). Characteristics of these techniques with basic principles of the
methodology, advantages and disadvantages are presented in Table 3. For the
future, the challenge is to study the cortical sensory and motor control of
gastrointestinal tract by evaluating brain to gut pathways using noninvasive
methods such as transcranial magnetic stimulation (TCMS) (43).
### Table 3. Characteristics of functional brain imaging techniques [according to (43)]

<table>
<thead>
<tr>
<th>Technique</th>
<th>Methodology</th>
<th>Temporal resolution</th>
<th>Spatial resolution</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>fMRI</td>
<td>Cerebral blood flow is measured by detection of oxygen concentration in areas of heightened neural activity exploiting the diamagnetic properties of oxyhemoglobin</td>
<td>4-8 s</td>
<td>~2 mm</td>
<td>Safety, radioisotopes not required</td>
<td>Artifacts produced by bony cavities and clusters of large blood vessels or changes in head position</td>
</tr>
<tr>
<td>PET &amp; SPECT</td>
<td>Cerebral blood flow is measured using positron emitting radioisotopes in PET (e.g., labeled water or fluorodeoxyglucose) or gamma-emitting isotopes in SPECT ((^{99m})Tc)</td>
<td>40 s</td>
<td>2-3 mm</td>
<td>Subcortical neurons can be detected Ligands can be used to study brain neurotransmission</td>
<td>Radioactive compounds Quite expensive Long lasting half-life of (^{99m})Tc</td>
</tr>
<tr>
<td>CEPs</td>
<td>Electrical manifestation of the brain’s response to external stimulus is recorded by surface scalp electrodes placed in relation to fixed anatomic landmarks</td>
<td>(10^{-3}) s according to the method</td>
<td>Safety Inexpensive and available equipment</td>
<td>Quality influenced by many variables (environmental, technical, psychological) Time consuming preparation of subject Interindividual variability in the conductivity of intervening tissue</td>
<td></td>
</tr>
<tr>
<td>MEG</td>
<td>Time-varying magnetic fields generated by current flow in the brain microcircuits are detected by magnetometers (superconducting wire loops)</td>
<td>(10^{-3}) s</td>
<td>1-5 mm</td>
<td>Magnetic field contrary to electrical fields are much less distorted by the conductivity of intervening tissue No preparation of subject is required</td>
<td>Expensive equipment - extremely sensitive detectors required Subcortical neurons are not readily detectable</td>
</tr>
</tbody>
</table>

fMRI, functional magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computerized tomography; CEPs, cortical evoked potentials; MEG, magnetoencephalography;
Since the results published in 1997 by Silverman et al. (44), neuroimaging has begun to provide evidences of physiological differences in central processing between normal individuals and patients with functional digestive disorders, although some contradictory and confusing results were obtained. Generally, an exaggerated activation of the vigilance network (prefrontal and cingulate cortices) or deactivation of regions involved in pain inhibition in IBS patients were suggested to lead to visceral hyperalgesia (45–47).

In an attempt to systematize neuroimaging data during visceral perception a comprehensive review was done by Debryshire (48). The results of fifteen relevant articles were analyzed according to stimulus, region and study population. Activation site were found to be reasonably well clustered within stimulus modality, suggesting consistent brain response to visceral sensation. Generally, the differences in reported activation during esophageal and lower gastrointestinal sensation imply altered motor, autonomic, and affect response during distension at opposite ends of the gastrointestinal tract (48).

Furthermore, the use of spinal monitoring and brain imaging techniques may enable to discriminate those patients who have gut hypersensitivity due to sensitization of primary visceral afferents and/or the spinal cord from those who have aberrant brain processing of sensation, as such a distinction may have therapeutic implication (43).

MODULATION OF VISCERAL SENSATION

The determinants of visceral sensitivity include the combined effect of subject’s characteristics, physiological, environmental, as well as methodological factors (Fig. 1).

Various neural, endocrine, and immune mechanisms operate along the brain-gut axis. Visceral sensory thresholds increase with age in healthy subjects (49). Differences owing to gender have recently been confirmed by studies using brain imaging techniques (50). Intraindividual variation of visceral sensitivity seems to be dependent on the severity of clinical symptoms and disease activity (51). In women with IBS, but not healthy volunteers, rectal sensitivity is affected by the menstrual cycle (52). Generally, in postprandial state visceral sensitivity is increased (31). Pharmacological modulation of gut wall tone has also been found to alter the perception of distension (18).

Technical conditions, methods of stimulation, and interaction of different stimuli may also affect results of studies. Perception can be modified by previous or simultaneous stimuli (53), the speed of distension (12), and the length of the gut stimulated (53). Extrinsic mechanisms having influence on perception include somato-visceral interaction, sympathetic arousal, and cognitive-affective phenomena (11, 54, 55).

Mental attention has been shown to increase perception to gastrointestinal stimuli (56), and hypervigilance for visceral stimuli is observed (57). Listening
tasks designed to be stressful increase the sensitivity of the colon to balloon
distension compared with relaxing music both in healthy subjects (55) and IBS
patients (58). Additionally, hypnotherapy (59), hypnosis (60) or treatment with
amitriptyline (61) were found to cause significant changes in rectal sensitivity in
IBS patients.

**Pharmacological studies**

Numerous mediators and pharmacological agents at different levels of the
brain-gut axis have therapeutic potential in the treatment of visceral
hypersensitivity (*Table 4*) (19, 62, 63). Serotonergic, non-serotonergic,
peripheral or central mechanisms may be distinguished in modulation of visceral
sensation. Serotonin is a key signalizing molecule in the gut released mainly from
the enteroendocrine cells by luminal stimuli. Several 5-HT receptor subtypes
have been identified. 5-HT3 antagonists (granisetron, alosetron, cilansetron) and
5-HT4 agonists (tegaserod, prucalopride) seem to have particular therapeutic
potential in the treatment of gastrointestinal sensorimotor dysfunctions.
Currently, application of selective serotonin reuptake inhibitors (SSRIs)
(paroxetine, citalopram) in the treatment for functional digestive disorders is
being assessed in prospective studies (64). Tricyclic antidepressants (e.g.,
amitriptyline), acting probably not only at the central level but also peripherally,
are already widely used in the treatment for IBS (65). Visceral sensitivity, as
assessed by rectal or colonic distension in humans, is reduced by opioids - µ, δ,
κ agonists (e.g., loperamid, fedotozine). The α2-adrenoceptor agonist -
clonidine, as well as somatostatin or oxytocin have also been shown to act as
visceral analgesics (19). Other putative agents reducing visceral sensitivity
include cholecystokinin antagonists, antagonists of tachykinin receptors,
dopamine-2 antagonists, or central cytokines. Drug trials based on the evaluation of visceral sensitivity have particularly important therapeutic implications.

Clinical applications

Methods for visceral sensitivity testing have still limited clinical application. Their variable sensitivity and uncertain specificity restrain from using them as clinical tools for diagnostic purposes. These methods are often time consuming, relatively expensive or invasive. Generally, as valuable research tools they have precise indications and restricted use in experienced laboratories.

More simple esophageal sensory testing including acid perfusion test (Bernstein test), provocation tests with betanechol or edrophonium, and balloon distension test may be to some extent useful in differential diagnosis of noncardiac chest pain, gastroesophageal reflux disease or functional dyspepsia (8). These methods are available and safe, but their sensitivity and specificity leave much to be desired.
Testing of visceral sensitivity in the diagnosis of functional gastrointestinal disorders, in particular functional dyspepsia and IBS, is still intensively discussed. Patients with functional dyspepsia have visceral hypersensitivity and alerted viscerovisceral reflexes that modulate gastric tone (42). Dyspeptic symptoms are probably related to this combined sensory and reflex dysfunction. At the same time, heightened visceral sensation both in patients with functional dyspepsia and IBS has been shown to be not site specific (66). Visceral sensitivity has been suggested to be a biological marker in IBS patients (13). Based on that Bouin et al. (67) proposed rectal distension test to be a diagnostic tool in IBS. However, this test does not fulfill expectations not allowing the positive diagnosis of IBS. Moreover, visceral hypersensitivity, although frequent, is not a constant finding among patients with IBS and may fluctuate (68). Relevant, but still remaining unclear, is an association between sensory dysfunctions and severity of symptoms.

In conclusion, since the landmark description of colonic hypersensitivity published by Ritchie in 1973 (69), results of numerous studies testing visceral sensitivity have provided a new insight into the brain-gut interactions and pathophysiology of functional gastrointestinal disorders. Nowadays, most of the modern techniques are applied in experienced laboratories, but the integration of basic and clinical research is in process. Assessment of visceral sensitivity may have some diagnostic application and practical use in evaluation of treatment effectiveness. The target is to develop noninvasive, reproducible and easily applicable methods. What is of cardinal importance is standardization of the experimental procedures to enable comparisons between results of different studies.

REFERENCES


