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PLENARY LECTURES

Reflex pathways controlling recto-anal evacuatory motility

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Because of the clinical and social impact of diseases in the large intestine (tumours, inflammation, and nerve degeneration) the motor activity of the recto-anal part of the gut is a matter of increased interest. The recto-anal evacuatory mechanism is a complex process involving the voluntary control of excretion as well as the myogenic properties of smooth muscles in the recto-anal region and the innervation of the rectum and internal and external anal sphincters.

The main injury in the recto-anal evacuatory process is the anal incontinence which is a status of inability of anal sphincters to restrain the discharge of the rectal content. Anal incontinence affects people of all ages but it is not an obligatory accompanying part of aging. This disorder is more common in women than in men because of trauma of the anal muscles and nerves that can occur during childbirth and more in older adults than in younger adults as the muscles that control bowel movement (anal sphincters) weaken. Subjects related to anal incontinence are often beset by feeling of shame, refuse to seek medical help and instead attempt to self-manage the problem which can lead to social withdrawal and isolation. Many people resort to altering their physical and social activities, even their employment, to cope with the problem. Anal incontinence affects about 10 % of the U.S. population. Such effects may be reduced by undergoing prescribed treatment, taking prescribed medicine and making dietary changes, expedient drug treatments and social procedures and by determining the mechanisms underlying the changes in the physiological balance of the recto-anal evacuatory motility (1).

The normal control of bowel movement depends on proper functioning of the smooth muscle layers of the colon and rectum, the muscles surrounding the anal aperture (internal and external anal sphincters), the brain centres of voluntary control and the body nervous system. Obviously, the physiological evacuatory process depends mainly on the properties of colo-recto-anal muscles and on the reflex pathways underlying the motor events.

The colo-recto-anal region is regulated by a dual nerve supply, somatic and autonomic (2). Mechanographic and electrophysiological observations demonstrate that the motor activity of the mammalian large intestine occurs also in isolated preparations, thus indicating that reflex pathways underlying the motility of the distal part of the gut are contained within the gut wall (3–6).

Despite of the analysis of gut motility has advanced considerable the interaction of activity in longitudinal and circular muscles is not fully understood and is a matter of studying. The functional coordination of the movements, contraction or relaxation, in both layers is not clear. It is believed that the spontaneous smooth muscle activity depends on the functional purposes of the gut region. In the small intestine the food bolus moves in a step-wise fashion while in the large intestine the content can be transmitted for long distances by giant propagated contractions. The migrating motor complex and spontaneous giant contractions in the distal colon have been attributed to the contractile activity of circular muscle. The circular muscle showed spontaneous activity composed of two types of contractions: low-frequency and high amplitude contractions with superimposed high-frequency and small-amplitude contractions. The coordination of motor activity of the longitudinal and circular muscles in the distal part of the gut and anal sphincters is not clear and the specific role of both muscles in the spontaneous and evoked motor events characterizing the evacuatory motility has not been identified.

We have re-examined colonic and recto-anal motility using a rat large intestine model-preparation consisting of colonic and recto-anal isolated segments mounted in flat partitioned organ bath(7). In particular, we were interested in evaluating the spontaneous and induced contraction and/or relaxation activity to display functional coordination between the colonic and rectal longitudinal and circular muscles and the anal sphincters.

The smooth muscles of colon, rectum and anal canal produced spontaneous high-amplitude contractions. The colonic contractions appeared synchronously in the longitudinal and circular muscles suggesting co-activation of nervous pathways supplying both muscles. The contractions arose in the proximal part and propagated to the distal part of the preparation indicating the involvement of descending excitatory pathways. Similar to the colon, the spontaneous activity of rectum demonstrated synchronization of high-amplitude contractions in both muscles, probably due to activation of descending colo-rectal excitatory pathways. The giant migrating contractions of the colon can propagate to the rectum and anal sphincters (8). The rectal contractions were followed by contractions of anal canal thus demonstrating a descending recto-anal excitatory reflex. It is likely that activation of the rectum can elicit recto-anal neuronal circuitry to organize coordinated descending motor activity in the longitudinal and circular axis.

The application of electrical field stimulation either to the proximal or to the distal part of colonic or recto-anal preparation elicited TTX-sensitive, i.e. neurogenic by nature, motor responses of the stimulated part. The responses were considered as result of local excitation of modular nervous structures (9). Local response of the longitudinal muscles of colon and rectum was contraction while the circular muscle of colon responded with relaxation followed by contraction. There were no differences between the relaxations of circular muscle in proximal or distal part of colonic preparation. The contractile component of the responses in the circular muscle was considerably less pronounced than that in the longitudinal muscle suggesting predominant excitatory activity of longitudinal muscle in colonic motility.

The local response of the internal anal sphincter was a short-lasting contraction followed by a relaxation while the anal canal responded with contraction thus suggesting that a modular neural circuit subserving the sphincter region controls the sphincter contraction/relaxation mechanism. The contractile responses of longitudinal muscle and the contractile components in the responses of circular muscle increased from colon to rectum while the relaxation responses were relatively uniform indicating a higher contractile potency than relaxation ability in colo-recto-anal tube (10).

Recently we evaluated the ascending motor responses of the longitudinal and circular muscle of rectum and the descending motor responses of anal sphincters as a display of functional characterization of reflex motor pathways subserving recto-anal evacuation (11). Electrical stimulation applied either to the anal or to the rectal part of the rat recto-anal segment elicited local motor responses of the stimulated part of preparation. At the same time ascending or descending motor responses of the contra-lateral, non-stimulated part were obtained, indicating that locally induced nerve activation propagated via intrinsic ascending or descending pathways. Contractile ascending motor responses of the longitudinal and circular muscle of rectum and contractile descending motor responses of the internal anal sphincter or the anal canal were observed demonstrating that neuronal and neuromuscular communications provided excitatory responses in both oral and anal directions in recto-anal tube. An ano-rectal excitatory reflex which produced rectal contraction upon stimulation of anal stretch receptors has been recently described in human and was suggested to be a second defecation reflex whereas the recto-anal inhibitory reflex was the primary reflex (12). We found that the ascending contractile motor responses were more pronounced than the descending motor responses when compared to the respective local responses thus suggesting that the nerve activation was expressed more in the ascending than in the descending recto-anal reflex pathways. Our data obtained in large intestine are in accordance with experiments performed in small intestine showing that the contractions of longitudinal and circular muscles induced by electrical or mucosal brush stimulation applied anally to the recording point were higher as compared to the responses to orally applied activation. The finding that the magnitude of the ascending responses of rectal longitudinal and circular muscles and the descending response of anal canal were less expressed as compared to the local responses supported the view that the propagation of excitation in nerve structures declined depending on the distance from the application of stimulation.

Both local and ascending contractile responses were more pronounced in the longitudinal muscle than those in the circular muscle, probably related to the functional purposes. Whereas the colon is considered as a site of faecal storage, there is controversy regarding the function of the rectum as a conduit or as a reservoir. The prevalence of contraction or relaxation events in the rectal motor activity is not clear. Our findings showing a dominant excitatory activity and efficacy of longitudinal muscle in the regional rectal motility suggest an essential role of this muscle layer in the contractile evacuatory mechanisms (13).

The internal anal sphincter responded to locally applied electrical stimulation with an initial contraction followed by a relaxation. The local response of the anal canal was a high-amplitude contraction. Atropine inhibited but not prevented the contractile responses suggesting that excitatory neurotransmissions except for the cholinergic one are involved in the sphincters motor activity. Contractile responses of internal anal sphincter elicited by electrical field stimulation or induced by adrenergic agonists were more recently described in dog, monkey and human and Substance P was proposed as exciting mediator of rat internal anal sphincter.

Surprisingly, a descending relaxation as a component of recto-anal inhibitory reflex was not observed of the internal anal sphincter response in drug-untreated preparations, probably due to the fact that electrical stimulation was applied to nutrient solution filled rectum without solid pellets. It is likely that recto-anal inhibitory reflex, i.e. descending relaxation of the internal anal sphincter could be activated in response to rectal distension when afferent neurons sensitive to mechanical stimuli were involved.

It is believed that the physiological significance of the recto-anal evacuatory activity could be mainly attributed to the autonomic recto-anal inhibitory reflex underlying the functional nature of rectal discrimination. The recto-anal inhibitory reflex consists of distension-evoked rectal reflex contraction and a synchronous internal anal sphincter reflex relaxation showing the importance of the propulsive capacity of the internal anal sphincter.

The contribution of recto-anal neurotransmission to the contractile and/or relaxant activity of internal and external anal sphincters requires further elucidation. According to Bharucha (2) both anal sphincters are responsible for maintenance of the neurogenic recto-anal motility. We failed to find experimental data demonstrating coordination of the rectal autonomic nerve pathways with the motor responses of the anal canal in the presence of preserved anatomical and functional integrity of internal and external anal sphincters. What is why we re-examined reflex evacuatory activity in the recto-anal region using balloon inflation-induced local distension of the rectal wall at a different distance from the anal canal as a display of the topography of descending motor reflex pathways controlling the evacuatory motility of anal sphincters integrity (14).

We observed that the motor response of the anal canal was dependent on the localization of the rectal wall distension which induced contraction or relaxation when applied far off or nearby the anal canal, respectively. This finding demonstrates locality-dependence of anal sphincters reflex motility. The differences in the pattern of responses suggest that distension-activated mechanoreceptors located along the rectal wall communicate with different neurotransmission consecutively acting during the evacuatory process. It could be assumed that physiological topography of the recto-anal descending motor reflex involves topical distribution of longer excitatory cholinergic and non-cholinergic pathways situated along the rectum providing contraction and shorter inhibitory mainly nitric oxide-dependent pathways located predominantly in the anal area underlying relaxation of the anal canal. The balloon inflation used imitates the distension evoked by stools in physiological conditions and it could be suggested that depending on its position along the rectum the rectal content initiates different phases of the recto-anal evacuatory mechanism.

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Aim: To evaluate the efficacy of intravitreal bevacizumab injection in reduction of the central macular thickness (CMT) in patients with diabetic retinopathy (DR) and branch or central retinal vein occlusion (BRVO, CRVO).

Patients and methods: In a prospective study, we included 107 eyes of 88 patients (33 male and 55 female) with proliferative DR, type 2 diabetes and 41 eyes of 34 patients (15 male and 19 female) with BRVO. All patients were treated with intravitreal bevacizumab 1.25 mg/0.1 ml. All eyes were followed-up at 4 weeks post-treatment. Best-corrected visual acuity (BCVA) was measured at baseline and 4 weeks post-treatment. OCT measurements were taken at baseline and 4 weeks post-treatment. We also performed fluorescein angiography at baseline and 4 weeks post-treatment. All patients were followed-up for 12 weeks. The mean age was 65.2 years (range 55-78 years). The mean duration of diabetes was 12.5 years (range 5-25 years). The mean CMT at baseline was 412.5 µm (range 374-451 µm). The mean CMT at 4 weeks post-treatment was 382.5 µm (range 348-416 µm). The mean BCVA at baseline was 0.5 (range 0.2-1.0) and at 4 weeks post-treatment was 0.6 (range 0.3-1.0). The mean CMT at 4 weeks post-treatment was significantly lower than at baseline (P < 0.001). The mean BCVA at 4 weeks post-treatment was significantly better than at baseline (P < 0.001). There were no significant side effects of intravitreal bevacizumab.

Conclusion: Bevacizumab seems to minimize the reduction of the CMT in patients with DR and BRVO. These results are encouraging and merit further investigation in larger scale studies.

Keywords: Central macular edema (CME), Visual acuity (VA), Bevacizumab (Avastin), Diabetic retinopathy (DR), Branch retinal vein occlusion (BRVO), Central retinal vein occlusion (CRVO).

Parameter	Baseline	4 weeks post-treatment
Mean CMT (µm)	412.5	382.5
Mean BCVA	0.5	0.6

Introduction: Although of differing aetiologies, both diabetic retinopathy (DR) and retinal vein occlusion (RVO) are associated with vessel impairment due to retinal ischaemia, vascular oedema, non-vascular vitreous haemorrhage, and possible retinal neovascularization (1, 2). The ischaemia of RVO commonly results from narrowing of intravitreal crossing and consequent retinal ischaemia (3), while in DR retinal vascular ischaemia, leading to capillary blockage and damage to the retinal vasculature, is believed to be a major contributing factor (4). Laser photocoagulation is an established therapeutic option to reduce the macular oedema in patients with DR, branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) (5, 6). However, over the past 15 years, significant attention has been directed towards the development of novel therapies for the treatment of retinal vascular disease. One such approach is the use of anti-vascular endothelial growth factor (VEGF) in promoting both macular vascularization and regression of retinal ischaemia (7). VEGF is a family of proteins that is secreted by the endothelial cells and is responsible for the regulation of the vascular endothelial growth factor (VEGF) in promoting both macular vascularization and regression of retinal ischaemia (7). VEGF is a family of proteins that is secreted by the endothelial cells and is responsible for the regulation of the vascular endothelial growth factor (VEGF) in promoting both macular vascularization and regression of retinal ischaemia (7). VEGF is a family of proteins that is secreted by the endothelial cells and is responsible for the regulation of the vascular endothelial growth factor (VEGF) in promoting both macular vascularization and regression of retinal ischaemia (7).

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