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• BRIEF REPORTS •

Effects of neurotrophins on gastrointestinal myoelectric activities of rats

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Abstract

AIM: To observe the effects of mouse nerve growth factor (NGF), rat recombinant brain derived neurotrophic factor (rm-BDNF) and recombinant human neurotrophin-3 (rh-NT-3) on the gastrointestinal motility and the migrating myoelectric complex (MMC) in rat.

METHODS: A randomized, double-blinded, placebo-controlled experiment was performed. 5-7 days after we chronically implanted four or five bipolar silver electrodes on the stomach, duodenum, jejunum and colon, 21 experimental rats were coded and divided into 3 groups and injected NGF, rm-BDNF, rh-NT-3 or placebo respectively via tail vein at a dose of 20 $\mu g \cdot kg^{-1}$. The gastrointestinal myoelectrical activity was recorded 2 hours before and after the test substance infusions in these consciously fasting rats.

RESULTS: The neurotrophins-induced pattern of activity was characterized by enhanced spiking activity of different amplitudes at all recording sites, especially in the colon. In the gastric antrum and intestine, only rh-NT-3 had increased effects on the demographic characteristics of electrical activities ($P<0.05$), but did not affect the intervals of MMCs. In the colon, all the three kinds of neurotrophins could significantly increase the frequency, amplitude and duration levels of spike bursts, and also rh-NT-3 could prolong the intervals of MMC in the transverse colon (25±11 min *vs* 19±6 min, $P<0.05$). In the distal colon rh-NT-3 could evoke phase III-like activity and disrupt the MMC pattern, which was replaced by a continuously long spike bursts (LSB) and irregular spike activity (ISA) for 48±6 min.

CONCLUSION: Exogenous neurotrophic factors can stimulate gut myoelectric activities in rats.

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INTRODUCTION

Many basic studies have shown that neurotrophins play fundamental roles in the differentiation, survival and maintenance of peripheral and central neurons[1-5] and have suggested the possible use of neurotrophins as therapeutic tools for degenerative neuronal disorders[6]. Neurotrophic factors comprise nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5, and NT-6[7-9]. These factors signal their effects through specific tyrosine-kinase (trk) receptors[10,11]. In addition to the high sequence homology of neurotrophins, neurotrophic factors including NT-3, BDNF and NGF are also highly conserved across species (mouse, rat and human)[13].

In a clinical study of patients with a variety of neurologic disorders treated with rh-NT-3 or recombinant human BDNF (rh-BDNF), they were found to have alterations of bowel function, and a dose-related tendency to increasing frequency of stools or having "diarrhea"[14]. Studies also have proved that exogenous neurotrophic factors stimulate gut motility and accelerate colonic transit in health and constipation[14]. This suggests that the action of rh-NT-3 and rh-BDNF on the gastrointestinal tract parallels their effect on the central nervous system. Review of the clinical reports suggested an increased frequency of bowel movements with less impressive effects on stool consistency[15], but the mechanism is unclear so far.

All the conclusions of previous studies lead to the hypothesis that neurotrophins alter bowel motor function, leading to increased frequency of bowel movements. In order to assess the action of neurotrophins on gut motility, in the present study we injected respectively NGF, rm-BDNF and rh-NT-3 via tail vein and registered the electrical activities with chronically implanted electrodes in fasting rats.

MATERIALS AND METHODS

Animal preparation

21 healthy Sprague-Dawley (SD) rats, weighing 250-300 (mean 276±17) g, 15 male and 6 female, individually housed, fed on chow pellets and water *ad libitum*, were used for these experiments. After fasted for 24 h, the rats were intraperitoneally anesthetized with sodium pentobarbital 30 $mg\cdot kg^{-1}$ (ip) A segment of the small intestine was exposed through a midline incision. Four or five bipolar insulated silver electrodes made by teflon-coated wire (0.5 mm in outer diameter, 20 cm in length) were implanted into the muscular layer of the bowel with a needle as a trocar. 1 mm of the wire was exposed near the implanted end, and the interval between pairs of electrodes should be 2.0-3.0 mm. The electrodes were placed on the gastric antrum at 5 mm proximal to the pylorus, on the duodenum and jejunum respectively at 5 cm and 20 cm distal to the pylorus, and on the transverse colon 5 cm distal to the ileocaecal junction. Among the 21 experimental animals, 9 were implanted electrodes on the distal colon 10 cm distal to the ileocaecal junction at the same time. The bundled electrode wires were grasped by the clamp through a silastic tube (2.4 mm in diameter), which then passed

through the subcutaneous tunnel from the abdominal incision to the back of the shoulder exit. Following surgery, the rats were individually housed, and allowed 5 to 7 days to recover from the surgery.

Motility recordings

The animals were fasted for 8 h with free access to water. The experiments were performed in conscious rats. The electromyographic (EMG) recordings were monitored by using a polygraph (Biolap98, Chengdu, China), with time constant set at 0.01 s, gain set at 1 000, the filtering at lower and higher frequencies set at 0.3 Hz and 100 Hz, respectively. The amplitudes of contractions were recorded in microvolts and the paper speed was 5 cm· h^{-1}.

Experimental procedure

A randomized, double-blinded, placebo-controlled experiment was performed. The rats were coded and divided into 3 groups, 7 animals in each group. On each experimental day, at the beginning of the experiments, the gastrointestinal myoelectrical activity was recorded for 2 h for each rat, and during this period at least 3 MMCs appeared. Then, the test substances were infused through the tail vein. The substances were dissolved immediately before use in normal saline. In each group, 2 rats were placed as control that received placebo (vehicle), 0.2 mL saline containing 250 μg bovine serum albumin (BSA, Sigma), the other 5 received 0.2 ml saline containing neurotrophins at a dose of 20 μg· kg^{-1}. Of them, 3 were placed electrodes on the distal colon as well. The three groups were injected them NGF (Sigma), rm-BDNF (Sigma) and rh-NT-3 (Sigma), respectively. After tail vein injection, the gastrointestinal myoelectrical activity of the rats was continuously recorded at least for 2 h. The codes of rats were not released (sealed) for analysis until all the EMG recordings and the entire data set for statistical studies were completed.

Statistical analysis

The results were expressed as $\bar{x}\pm s$ unless otherwise stated. Student' s *t* test was used to compare the different paired values before and after the test substance administration in the 3 groups. It was considered to be statistically significant when $P<0.05$.

RESULTS

Gastrointestinal myoelectrical activity during fasting

About 1 week later, among the 93 pairs of electrodes, 2 pairs implanted on the gastric antrum failed possibly due to the their slipping off, the other 91 pairs continued to function until the study was completed. A typical pattern of myoelectrical activity in the fasting state was observed in all rats (Figure 1, Table 1). Of the totally 238 activity fronts recorded in fasting rats under control, we observed that 199 (80 %) started in the duodenum.

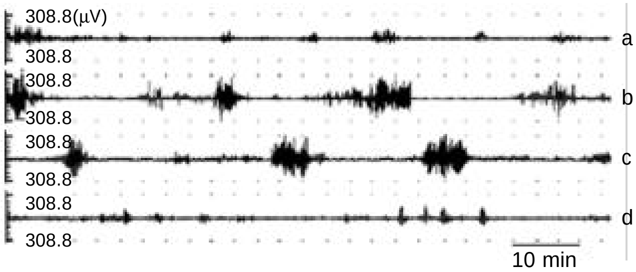

Figure 1 Electrical activity recorded directly from four electrode sites on the gastric antrum (a) at 5 mm proximal to the pylorus, on the duodenum (b) and jejunum (c) respectively at 5 cm and 20 cm distal to the pylorus, and on the transverse colon (d) at 5 cm distal to the ileocaecal junction in one fasting rat.

The antral myoelectrical activity was characterized by the presence of spike bursts, superimposed at 34.5 % of the

Table 1 Effects of neurotrophins (20 μg·kg^{-1}) on gut myoelectric activity profiles 2 h before and 1 h after administration. ($\bar{x}\pm s$)

Parameter	Site	n	NGF treatment		rm-BDNF treatment		rh-NT-3 treatment		Placebo treatment	
			Before	After	Before	After	Before	After	Before	After
Frequency of spike bursts (min^{-1})	Antrum	5	1.6±0.5	1.6±0.5	1.6±0.5	1.6±0.5	1.6±0.5	1.8±0.6[a]	1.6±0.5	1.6±0.5
	Duodenum	5	16.2±5.4	17.5±5.8	15.9±5.2	17.2±5.9	16.3±5.6	20.1±9.3[a]	16.3±5.4	16.5±5.6
	Jejunum	5	12.1±2.8	13.5±3.4	11.9±2.6	13.2±3.7	12.2±2.7	16.5±7.1[a]	12.5±2.9	12.4±2.8
	Transverse colon	5	0.6±0.1	0.8±0.1[a]	0.6±0.1	0.8±0.1[a]	0.6±0.1	0.9±0.2[b]	0.6±0.1	0.6±0.1
	Distal colon*	3	0.5±0.1	0.7±0.1[a]	0.5±0.1	0.7±0.1[a]	0.5±0.1	0.9±0.2[b]		
Amplitude of spike bursts (μV)	Antrum	5	180.2±18.6	182.3±19.1	181.3±17.9	182.5±20.4	180.6±17.9	185.2±22.1[a]	180.9±18.8	180.4±18.9
	Duodenum	5	306.5±73.6	308.8±72.7	306.7±72.9	308.4±72.4	306.5±72.7	314.6±81.8[a]	305.6±74.2	306.2±74.5
	Jejunum	5	295.8±87.2	297.4±88.5	296.5±88.1	298.6±89.3	295.6±86.7	313.8±98.3[b]	296.8±87.3	295.8±88.5
	Transverse colon	5	138.7±32.1	142.5±35.9[a]	139.4±33.4	145.5±38.8[a]	139.5±33.3	160.3±47.5[b]	137.9±31.8	139.1±32.5
	Distal colon*	3	142.9±29.9	163.5±40.1[a]	141.2±27.3	160.5±37.4[a]	142.6±29.1	173.4±35.4[b]		
Duration of spike bursts (s)	Antrum	5	4.8±1.1	4.8±1.2	4.7±1.2	4.9±1.3	4.8±1.2	4.9±1.5	4.8±1.2	4.8±1.2
	Duodenum	5	6.5±2.7	6.6±3.1	6.5±2.8	6.6±3.2	6.5±2.8	11.5±6.8[a]	6.5±2.8	6.5±2.7
	Jejunum	5	6.7±3.1	6.8±3.2	6.7±3.1	6.9±3.4	6.8±3.2	12.9±8.3[a]	6.8±3.2	6.8±3.2
	Transverse colon	5	9.3±2.2	14.3±6.2[a]	9.3±2.2	13.5±7.2[a]	9.3±2.3	15.3±7.5[a]	9.3±2.2	9.3±2.3
	Distal colon*	3	12.7±2.7	17.8±3.8[a]	12.7±2.7	19.7±4.7[a]	12.7±2.8	46.2±7.3[b]		
Intervals of MMC (min)	Antrum	5	10.1±3.1	11.3±4.0	10.2±3.4	11.3±4.3	10.1±3.1	12.3±6.2	10.3±3.3	10.2±3.1
	Duodenum	5	15.3±5.4	16.9±6.1	16.1±5.5	17.2±6.2	15.5±5.5	17.3±7.5	15.6±5.5	15.6±5.2
	Jejunum	5	16.8±5.8	18.2±7.4	17.1±5.9	18.9±7.6	16.8±5.8	19.1±9.1	16.4±5.6	16.4±5.6
	Transverse colon	5	18.4±6.0	19.7±6.1	19.3±6.1	21.0±7.5	18.9±6.0	25.1±11.1[a]	19.2±6.2	19.7±6.3
	Distal colon*	3	19.7±4.1	22.2±8.0	20.8±5.3	23.5±8.4	19.9±4.2	-		

[a]$P<0.05$, [b]$P<0.01$ *vs* before, * There were 3 among 5 experimental rats in the three groups placed bipolar electrodes at distal colon.

rhythmic oscillatory potentials corresponding to the slow wave rhythm. In fasting rats, the pattern of spike bursts of the small intestine was organized into cyclic MMCs that occurred at regular 15.6±5.4 min intervals and were propagated from the duodenum to the jejunum at 2 to 3 cm· min^{-1}. Each MMC was a cycle consisting of four phases: a period of silence (slow wave), namely phase I lasting 7.3±0.8 min, which was followed sequentially by a period of ISA (irregular spike activity), namely phase II lasting 4.1±0.9 min, and phase III of intense RSA (regular spike activity) lasting 3.6±1.1 min. Phase IV was the last period from the end of phase III to the start of phase I lasting 0.9±0.3 min. The intervals between the MMCs were measured from the end of one activity before to the end of the next one.

The pattern of colonic myoelectrical activity was characterized by randomly occurring spike bursts at a frequency of 0.6±0.07 per minute in the transverse colon and 0.5±0.09 per minute in the distal colon.

Effects of neurotrophins on the gastrointestinal and colon myoelectric activity

The effect of neurotrophins on the gastrointestinal motility was established within 2 to 4 min after commencement of the infusion. The neurotrophin-induced pattern of activity was characterized by enhanced spiking activity of different amplitudes at all recording sites, especially at the colon, which continued about 50±8 min and gradually returned to normal complexes. There was no significant difference in demographic characteristics before and after placebo treatment. Table 1 summarizes the effect of neurotrophins on the different electromyographic parameters before and after treatment.

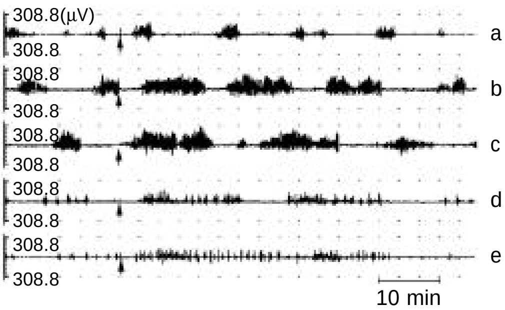

Figure 2 The effects of rh-NT-3 on the myoelectric activities respectively recorded from gastric antrum (a), duodenum (b), jejunum (c), transverse colon (d), and distal colon (e) in one case. The arrows indicated the time point of rh-NT-3 injection via tail vein at a dose of 20 μg · kg^{-1}.

In the gastric antrum and intestine of fasting rats, administration of 20 μg· kg^{-1} mouse NGF and rm-BDNF didn' t significantly increase electrical activities (P>0.05), whereas intravenous infusion of 20 μg· kg^{-1} rh-NT-3 could increase the frequency, amplitude and duration of spike bursts (P<0.05, Table 1), but did not affect the intervals of MMCs (Figure 2).

In the colon, treatment with mouse NGF and rm-BDNF prolonged the duration as well as increased the frequency and amplitude of spike bursts (P<0.05, Table 1) without alterations of MMC intervals. In the transverse colon, rh-NT-3 not only significantly increased the electrical activities, but also prolonged the intervals of MMC (25±11 min *vs* 19±6 min, P<0.05) (Figure 2). The distal colon electromyogram recordings in 3 cases implanted bipolar electrodes on the distal colon, showed that rh-NT-3 could evoke phase III-like activity and disrupt the MMC pattern that were replaced by a continuous long spike bursts (LSB) and irregular spike activity (ISA) for 48±6 min (Figure 2).

DISCUSSION

Previous studies showed that rm-BDNF and rh-NT-3 caused diarrhea in a dose-related manner[15] and that exogenous neurotrophic factors accelerated colonic transit and increased stool frequency in humans[14]. The present studies were carried out to evaluate comparatively the effects of NGF, rm-BDNF and rh-NT-3 on the gastrointestinal myoelectric activity in fasting rats. The study firstly showed that neurotrophin-induced pattern of activity was characterized by enhanced spiking activity of different amplitudes at all recording sites, especially in the colon. The MMCs were firstly described in the small intestine of fasting dogs and its presence was observed in several species, including rats. In the present studies, MMC was also observed in fasting rats and found that in gastric antrum and intestine, only rh-NT-3 had enhanced effects on demographic characteristics of electrical activities (P<0.05), but did not affect the intervals of MMCs. In the colon, not only all the three kinds of neurotrophins infusion could significantly increase the frequency, amplitude and duration of spike bursts, but also rh-NT-3 could prolong the intervals of MMC in the transverse colon (25±11 min *vs* 19±6 min, P<0.05), and in the distal colon, rh-NT-3 could evoke phase III-like activity and disrupt the MMC pattern, which was replaced by continuous LSB and ISA for 48±6 min. Thus the present results indicate that exogenous neurotrophic factors can stimulate gut myoelectric activity in rats. The recording of myoelectrical activity by means of chronically implanted electrodes in rats is a suitable experimental animal model to investigate the mechanism of action of neurotrophins on intestinal motility.

Our conclusion is consistent with the previous ones. Probably it can contribute to the explanation of the mechanisms of the rapid onset of diarrhea in clinical trials with these neurotrophins, that neurotrophins lead to increases of bowel motor, as a result the gastrointestinal contents are transmitted too quickly, leading to diarrhea for the water having not been fully absorbed.

Two mechanisms mediating the actions of neurotrophins on neuromuscular function are considered: trophic effects or a direct effect on neurotransmission[22]. The neurotrophins have long-term trophic actions, including prolongation of survival and speeding up phenotypic maturation of many types of neurons[16-19]. These functions are mediated by the Trk family of tyrosine kinase receptors[20-23]. Modulation of neurotransmission has been shown by acute or short-lived effects of neurotrophins[24,25]. For example, BDNF modulates neurotransmitter synthesis, increases neuronal excitability, and provides long-term synaptic potentiation of neurons[26], and it has been reported that NT-3 stimulates the expression of SP and neurotrophins, enhances not only synthesis but also storage of acetylcholine (Ach) in cultured septal neurons[27]. The time of the onset of effects on bowel movements with exogenous r-metHuBDNF and r-merHuNT-3 suggested direct actions on the neuromuscular apparatus or a very rapid trophic or regenerative effect on gut neuromuscular function. The other study suggested that the mechanism of rh-NT-3 excitation of colonic muscle involved increased noncholinergic contractility and decreased NANC neurotransmission with reduction in number of nitric oxide synthase (NOS) neurons. The abundance of BDNF protein in certain internal organs suggests that this neurotrophin may regulate the function of adult visceral sensory and motor neurons.

We are not quite clear why different enhancements of neurotrophins accelerating gut transition in the stomach, duodeno-jejunum and colon are possibly associated with the receptors of different neurotrophin distribution in gastrointestinal tract. Decreased trk C expression may reflect developmental abnormalities in Hirschsprung' s disease and idiopathic slow-transit constipation (STC)[28]. Further studies are needed to elucidate the precise mechanism by which neurotrophins influence smooth muscle contractility and/or enteric nerve functions in the human gastrointestinal tract.

Gut motility disorder is common in clinical practice[29-33], and its suitable treatment should be studied[34-38]. In this respect, our data indicate that neurotrophins are the promising agents capable of modifying transit in the entire gastrointestinal tract and may provide novel treatments for patients with disturbed gut motility, such as Hirschspnmg' s disease[28, 39].

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