

Serotonin & Serotonin-related Drugs in Functional GI Disorders

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세로토닌 (5-hydroxytryptamine, 5-HT)

⁴ 5-HT

가,

1.

5-HT 3-(beta-aminoethyl)-5-hydroxyindole
가

5-HT 5%

95%

5-HT 90% enterochromaffin (EC)
10%

(excitatory postsynaptic potential)

5-HT tryptophan

(hydroxylation)

(decarboxylation)

²

monoamine oxidase aldehyde dehydrogenase

oxide (NO)

nitric

5-HT가 5-hydroxyindole acetic acid (5-HIAA)

5-HT

5-HIAA 2-10mg/day

³

가

EC

5-HT가

2. 5-HT

5-HT

가

, 5-HT

5-HT

⁶

EC

5-HT

3. 5-HT

5-HT

, EC

9가

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5-HT 가

5-HT_{1A}, 5-HT_{1C}, 5-HT_{1P}, 5-HT₂, 5-HT₃

5-HT₄

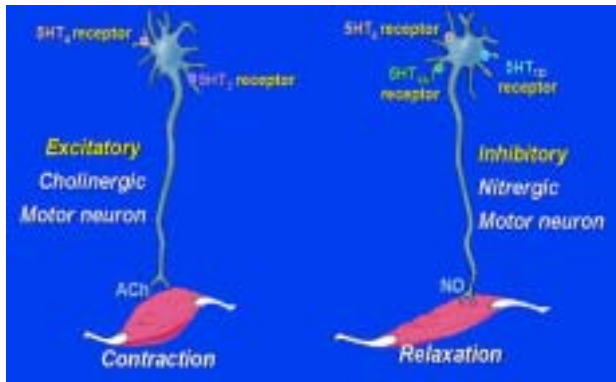


Fig. 1. Motor Function of the Serotonin Receptors subtypes in GI Tract.¹

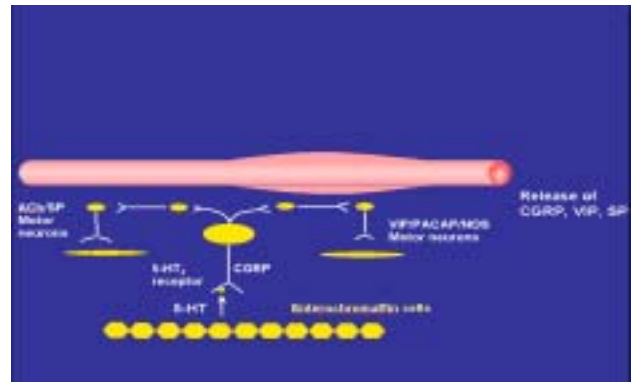


Fig. 2. Model depicting extrinsic and intrinsic sensory pathways mediating the peristaltic reflex.⁵

가
 5-HT₃ 5-HT₄ (Fig. 1).¹
 가
 ,
 . 5-HT₄
 ,
 (extrinsic visceral afferent)
 ,^{6,9} 5-HT₄ 가
 ,^{5,7,10}
 EC 5-HT가 ,
 5-HT가 calcitonin gene-related peptide (CGRP)
 5-HT₄
 CGRP가 , CGRP vasoactive
 intestinal peptide, NO
 , substance P
 (Fig. 2).⁵

5-HT₃
 .
 5-HT₃
 . Area postrema nodosa ganglion
 가
 가 5-HT가 ,
 . 5-HT₃
 가
^{11,12}
 2) 5-HT₄
 5-HT₄ adenylyate cyclase
 .
 5-HT₄ 가
 , 5-HT₄ 가 5-HT₄
 . 5-HT₄
 ,
 (Table 1).¹³

Table 1. 5-HT Receptors in the Gut

Subtypes	Species and localization	Cellular localization	Cellular function
5-HT ₃	Guinea pig ileum	Enteric nerves	Depolarization
	Rabbit, mouse small intestine	Enteric nerves	
	Rabbit, rat, cat	Vagus afferent nerve	Facilitate 5-HT release
	Guinea pig ileum	Enterochromaffin cell	
5-HT ₄	Guinea pig ileum	Enteric nerve (presynaptic)	Acetylcholine release
	Rat esophagus	Smooth muscle	Relaxation
	Guinea pig ascending colon	Enteric nerve (presynaptic)	Acetylcholine release
	Guinea pig ileum	Enterochromaffin cell	Inhibit 5-HT release

세로토닌 관련 약제들

5-HT

5-HT

5-HT

(Table 2).¹⁴

(IBS) 5-HT가

Bearcroft¹⁵ IBS 5-HT

5-HT 가 가

5-HT가

5-HT

5-HT 가

5-HT₃ 5-HT₄ 가

5-HT

IBS (Table 3).¹⁷

1. 5-HT₁

1) Buspiron

5-HT 5-HT_{1A} fast & slow

excitatory postsynaptic potential

buspiron 5-HT_{1A}

Table 2. Pharmacological actions of 5-HT compounds

Pharmacological actions	5-HT ₃ antagonist	5-HT ₄ antagonist
Accelerates upper GI transit	±	+
Increases colonic motor activity	-	+
Slows colonic transit	+	-
Anti-emetic (chemotherapy-induced)	+	?
Analgesic	+	?
Anxiolytic	+	?

, buspiron

5-HT_{1A}

가

5-HT_{1A}

18,19

2. 5-HT₃

5-HT₃

5-HT₃

5-HT₃ 가

5-HT₃ 가

5-HT₃

가

5-HT₃

IBS

1) Ondansetron, Granisetron, Tropisetron

Area postrema 5-HT₃

cisplatin EC 5-HT

5-HT₃

20

ondansetron, granisetron tropisetron . Ondansetron

IBS

Granisetron

가 , IBS granisetron

21

Table 3. Potential clinical role of 5-HT₃ receptor antagonists and 5-HT₄ receptor agonists

Disorder	5-HT ₃ antagonist	5-HT ₄ antagonist
Gastroesophageal reflux	-	+
Non-cardiac pain	+	-
Gastroparesis	-	+
Functional dyspepsia	+	+
Ileus	-	+
Pseudo-obstruction	-	+
Constipation-predominant IBS	-	+
Diarrhea-predominant IBS	+	-
Carcinoid diarrhea	-	-

Tropisetron

, 5-HT₄

가

²²

2) Alosetron

Alosetron 5-HT₃

. IBS

2004 Lembo ²⁸

alosectron 1 mg 2, 12

IBS

alosectron

²³

28%,

9%

가

alosectron

가

1

, Chey ²⁹

IBS

, 48

2 mg

²⁴ IBS

alosectron 4 mg

가

12

²⁵

, alosectron

IBS

가

가

FDA

2000

IBS

3) Cilansetron

5-HT₃

, 2005

20-30%

가

IBS

, 3

가

700-1000

1

^{30,31} Alosetron

²⁶

IBS

IBS

가, 2002 7

가

가

IBS

가

alosectron

3. 5-HT₄

5-HT₄

²⁷

'cross-talk' ()

5-HT

가 5-HT₃

가

5-HT₄

5-HT₃

5-HT가 가

5-HT₁

5-HT₂

5-HT₃

가

가

1) Tegaserod

Tegaserod aminoguanidine-indole

5-HT₄

³² Tegaserod

³³⁻³⁵

tegaserod가 5-HT₄

, tegaserod

5-HT

가

5-HT

, alosectron

가

⁵⁻⁷

가

tegaserod

5-HT₄ 가 32, 36 tegaserod가 , tegaserod 가 (Fig. 3). , tegaserod 5-HT₄ , tegaserod IBS 1 6 mg , 2 , 12 가 , 12% , 10% 37 2) Mosapride Mosapride 5-HT₄ 가 38 가 , 39 mosapride , , 가 , mosapride 가 , , 가 , (Fig. 4). , mosapride 5-HT₄

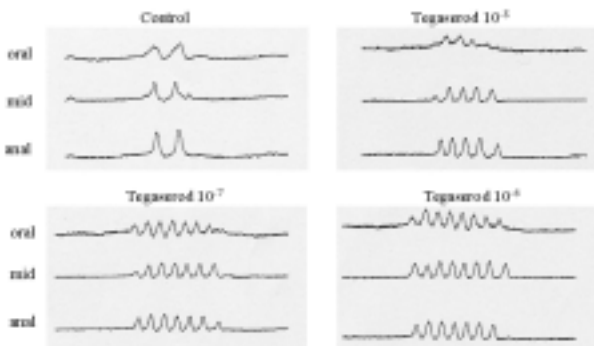


Fig. 3. The effect of tegaserod on ileal peristalsis. Tegaserod induces concentration-dependent increase in the number of peristaltic waves.

Serotonin transporter and serotonin selective reuptake inhibitors

1. Serotonin Transporter ()

(serotonin transporter, SERT) (synaptic cleft) 5-HT (presynaptic nerve terminal) (axonal varicosity) 5-HT 41,42 5-HT (Fig. 5).^{43,44} , SERT promotor 16 repeat element가 , 16 repeat element SERT SERT 5-HT .⁴⁵ SERT 2 가 , intron 17 variable number tandem repeats (VNTRs) short (S) long (L) 5'-flanking (SERT gene-linked polymorphic region) .⁴⁵

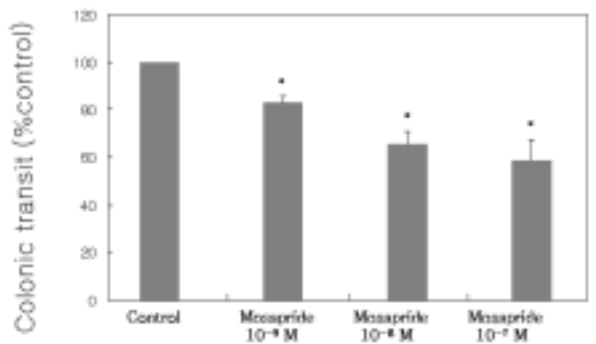


Fig. 4. The effect of mosapride on the colonic transit. Data are expressed as % change from the colonic transit time of control.³⁹ * p<0.05

(VNTR) , IBS , L/L, L/S, S/S 가 (Fig. 6). short (S/S) (L/S) L/L , 5-HT 가 .^{45,46} SERT IBS 가 ,⁴⁷ S/S 가 , S/S .^{48,49} Camilleri⁵⁰ IBS 가 (Table 4), SERT-P 가 IBS SERT promotor 5-HT₃ .^{50,51} 49 IBS 5-HT 가 , SERT 5-HT 가 , SERT

, IBS 5-HT SERT S/S, S/L, L/L 57.1%, 37.5%, 5.4% ,⁴⁶ 39.5%, 37.0%, 23.5%,⁵² 16%, 50%, 34% . 5-HT가 가 , 5-HT 가 S/S IBS 가 가, 5-HT 가 가 ,⁵³ Chen⁵⁴ SERT +/+ 5-HT 가 , SERT -/- , 가 가, 가 5-HT 가 5-HT (downregulation)

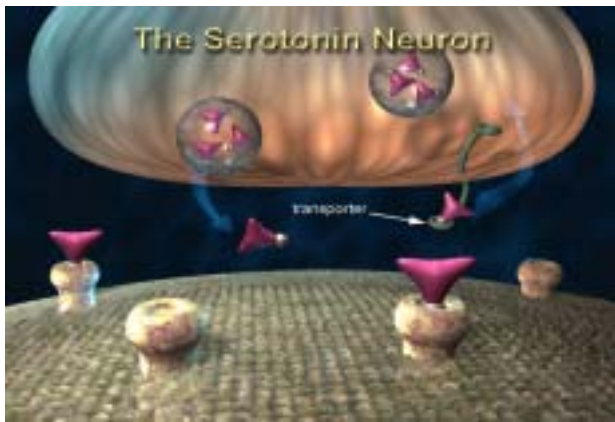


Fig. 5. Serotonin transporter.

Table 4. Polymorphism of the SERT-P region in the SERT gene in IBS patients according to their subtypes

Genotype	SERT Gene SERT-P Polymorphism		
	Diarrhea Predominant (n=27)	Constipation Predominant (n=13)	Diarrhea Constipation (n=13)
S/S	14 (51.9%)	10 (76.9%)	5 (38.5%)
S/L	12 (44.4%)	1 (7.7%)	6 (46.2%)
L/L	1 (3.7%)	2 (15.4%)	2 (15.4%)

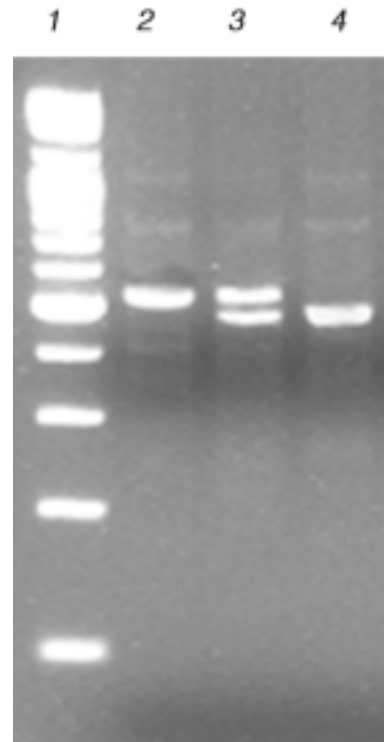


Fig. 6. Genotyping of SERT-P polymorphism by gel microchip electrophoresis. Lane 1, 100 bp sizing ladder;2, L/L homozygote (528 bp: 16 repeat);3, S/L heterozygote (484 bp: 14 repeat; 528 bp: 16 repeat);4, S/S homozygote (484 bp: 14 repeat).⁴⁸

2. (selective serotonin reuptake inhibitor, SSRI)

SSRI serotonin-transporter 5-HT
 ,⁵⁵ 5-HT 가 가
 , 5-HT , 5-HT₃ 5-HT₄
 , 5-HT
 가 , SSRI
 가 . SSRI
 , ,
 , fluoxetine
 가 가 , paroxetine
 가
 ,⁵⁶ IBS paroxetine 20-40 mg 12
 , , , ,
 IBS
 .⁵⁷ Citalopram paroxetine
 , IBS
 ,
 IBS
 .^{58,59}

Summary and Conclusion

5-HT
 가 5-HT
 , IBS IBS
 5-HT가
 ,
 ,
 가
 ,
 .

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