Combined Blockade of 5-HT$_3$- and 5-HT$_4$-Serotonin Receptors Inhibits Colonic Functions in Conscious Rats and Mice

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ABSTRACT
We have already reported that 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists failed to modify 5-HT-accelerated colonic transit in conscious rats, but the 5-HT$_3$ and 5-HT$_4$ receptor dual antagonist FK1052 prevented the enhancement. In this study, the inhibitory effect on the stimulated colonic transit was not also observed with 5-HT$_4$ receptor antagonists (SDZ205-557 and SB204070) in freely moving rats with chronic cannulas implanted into the proximal colon. In contrast, combined antagonism by simultaneous administration of ondansetron and the 5-HT$_4$ receptor antagonist exerted a drastic inhibitory effect on the propulsive motility. Furthermore, we examined the effect of 5-HT receptor antagonists on 5-HT-induced fluid secretion in mice. Although none of these selective 5-HT receptor antagonists (YM060 and ondansetron as 5-HT$_3$ receptor antagonist, SB204070 as 5-HT$_4$ receptor antagonist) by itself produced a great inhibition of the 5-HT-induced diarrhea, the combination of a 5-HT$_3$ receptor antagonist and a 5-HT$_4$ receptor antagonist markedly reduced the diarrhea. These data suggest that 5-HT-accelerated colonic motility and 5-HT-evoked fluid secretion are mediated by both 5-HT$_3$ and 5-HT$_4$ receptors and that the pathways activated by these receptors may collaborate.

Gershon et al. (1965) showed that 5-HT might be a neurotransmitter of the enteric nervous system. 5-HT is secreted from enterochromaffin cells of the epithelium in response to a variety of luminal stimuli, which activate the neuronal circuit within the gastrointestinal wall (Bulbring and Lin, 1958; Bulbring and Crema, 1959a,b). 5-HT has many different types of actions on the gut and, in particular, has been proposed to play a critical role in the mediation of the peristaltic reflex and in electrolyte transport by acting at 5-HT receptors in the enteric nervous system (Gershon et al., 1994; Cooke and Reddix, 1994).

Electrophysiological studies on GI motility have revealed the presence of at least three excitatory subtypes of 5-HT receptor (5-HT$_1P$, 5-HT$_3$ and 5-HT$_4$) on myenteric neurons of the guinea pig intestine (Mawe et al., 1986; Wade et al., 1994; Craig and Clarke, 1990; Pan and Galligan, 1994), but it is not yet clear which subtypes are of physiological significance in GI motility. The mediation of a slow excitatory response has been associated only with the 5-HT$_1P$ receptor (Mawe et al., 1986), which mediates the peristaltic reflex (Wade et al., 1996). 5-HT$_3$ receptors are ligand-gated cation-conducting channels that are present on neuronal cell bodies such as nicotinic receptors (Derkach et al., 1989), and presynaptic 5-HT$_4$ receptors probably mediate an enhanced release of ACh (Kilbinger and Wolf, 1992).

In terms of electrolyte transport, 5-HT is a strong secretagogue in the gut and produces an increase in I$_{sc}$ indicative of chloride secretion by stimulation of some 5-HT receptor subtypes. For example, it has been shown that the I$_{sc}$ response to 5-HT in guinea pig ileum consists of two components, one sensitive to TTX and mediated by 5-HT$_3$ receptors and the other insensitive to TTX and mediated in part by 5-HT$_4$ receptors (Scott et al., 1992), and that in guinea pig distal colon, the I$_{sc}$ is mediated by neural 5-HT$_3$ receptors (Cooke et al., 1991). On the other hand, in tissues such as rat colon (Bunce et al., 1991), human jejunum (Kellum et al., 1994) and ileum (Borman and Burleigh, 1993) 5-HT seems to induce an increase in the I$_{sc}$ by stimulating non-neural 5-HT$_4$ receptors. Thus there are many reports of in vitro studies showing an involvement of 5-HT$_3$ and 5-HT$_4$ receptors in secretion response to 5-HT, but few in vivo studies.

Many questions about enteric 5-HT receptors remain to be answered. These questions have only recently begun to be addressed, because an experimental approach using selective 5-HT$_3$ receptor antagonists and selective 5-HT$_4$ receptor antagonists has enabled us to investigate the role of 5-HT receptors in gastrointestinal function.

The purpose of this study was to determine, in animal

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ABBREVIATIONS: 5-HT, 5-hydroxytryptamine; TTX, tetrodotoxin; 5-HTP-DP, 5-hydroxytryptophyl-5-hydroxytryptophan amide; I$_{sc}$, short-circuit current; ENS, enteric nervous system.
models in vivo, whether 5-HT₃ and/or 5-HT₄ receptors are involved in colonic function and, if so, whether there are additive, synergistic or nullifying effects of activating or inhibiting these subtypes of enteric 5-HT receptor.

Materials and Methods

Animals. Male Sprague-Dawley rats (211–331 g; Charles River Japan, Hino, Japan) and male ddY strain mice (29–37 g; Japan SLC, Hamamatsu, Japan) were used in these studies. Before experiments, animals were housed under standard controlled environmental conditions, with 12-hr light/dark cycles. Animals were allowed at least 1 week to acclimate to the environment before the experiments were performed. The animals were allowed food and water ad libitum while housed. Mice, but not rats were deprived of food overnight before the experiment but were allowed free access to water.

5-HT-accelerated transit in rat colon. After rats were anesthetized with pentobarbital (50 mg/kg i.p.), a chronic indwelling polyethylene cannula (I.D., 0.58 mm; O.D., 0.97 mm; PE-50, Becton, Dickinson and Co., Parsippany, NJ) was implanted into the proximal colon about 1.5 cm from the ileocecal junction. The cannula was led s.c. to the interscapular region of the animal’s neck. The abdominal incision was closed with a suture. Rats were individually housed and allowed to recover from surgery for 5 days. The experiments were performed in conscious and freely moving rats. 5-HT (1 mg/kg) or normal saline was administered s.c. 20 min before gentle infusion of carmine red (0.3 ml; 3 g carmine red and 5 g arabic gum in 50 ml of 0.5% methylcellulose) as a nonabsorbable marker into the proximal colon through the implanted cannula. Ondansetron was administered p.o. and SB204070 or SDZ205-557 was injected s.c. 30 min before 5-HT administration. Twenty minutes after the injection of 5-HT (or saline in controls), the animals were sacrificed, and the entire colon was carefully and quickly removed. The length of colon marked by carmine red was measured and expressed as percent of total length of colon.

5-HT-induced diarrhea in mice. The experiments were carried out as previously reported (Kadowaki et al., 1993). Evaluation of diarrhea was made 15 min after the i.p. administration of 5-HT (0.32 mg/kg). Diarrhea was defined as wet and unformed stools and was scored as present or absent for each animal. The occurrence of diarrhea was noted, and the incidence of diarrhea (number of mice with diarrhea/total number of mice tested) was calculated as a percentage. 5-HT (0.32 mg/kg i.p.) caused diarrhea in 80% to 100% of the fasted mice within 15 min. Ondansetron and YM060 were administered p.o. and SB204070 was injected s.c. 30 min before 5-HT administration.

Statistics. Values for the experiments in rats represent mean ± S.E.M. Group data were compared by analysis of variance (ANOVA) followed by Dunnett’s Multiple Range test. Chi-square analysis was used in mice to compare the incidence of diarrhea and to determine the statistical significance of differences between the groups. Probability values ≤ .05 were considered statistically significant.

Drugs. Ondansetron, YM060, SDZ205-557 and SB204070 were synthesized by Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. 5-HT creatinine sulfate was purchased from E. Merck (Darmstadt, Germany). Ondansetron, YM060 and SB204070 were dissolved in distilled water. SDZ205-557 was initially dissolved in equivalent 0.1 N HCl and was then diluted in physiological saline. 5-HT was dissolved in saline. The drugs were administered at a volume of 2.0 ml/kg in rat and 5.0 ml/kg in mouse.

Results

Effect of 5-HT₄ receptor antagonist on 5-HT-accelerated colonic transit in rats. The submaximal effective dose (1 mg/kg) of 5-HT was used to examine the effects of the test drugs on 5-HT-accelerated colonic transit in rats, as reported previously (Kadowaki et al., 1993). 5-HT (1 mg/kg s.c.) accelerated the colonic transit of carmine red about 30% above the basal rate with vehicle alone (fig. 1). Two 5-HT₄ receptor antagonists, SDZ205-557 (≥ 3.2 mg/kg s.c.; fig. 1) and SB204070 (≥ 1.0 mg/kg; fig. 2), had no effect on 5-HT-accelerated colonic transit in conscious rats at moderately high concentrations. When the dose of SDZ205-557 was increased to 10.0 mg/kg, a significant inhibition (66%) was obtained (fig. 1), but at this concentration, SDZ205-557 may have other, nonspecific effects. It is notable that the more potent and selective 5-HT₄ receptor antagonist, SB204070, had no effect on the colonic transit.

Effect of the combination of ondansetron and 5-HT₄ receptor antagonist on 5-HT-accelerated colonic transit in rats. The inhibition of colonic transit that was observed after the administration of a high dose of SDZ205-557 (see the account above and Fig.) agreed with previous observations of the effects of FK1052 (Kadowaki et al., 1993). However, these drugs have activities at both 5-HT₃ and 5-HT₄ receptors. We therefore tested the hypothesis that both 5-HT₃ and 5-HT₄ receptors participate in the 5-HT-induced acceleration of colonic motility by employing the selective 5-HT₃ receptor antagonist ondansetron (3.2 mg/kg p.o.) and the selective 5-HT₄ receptor antagonist SDZ205-557 (3.2 mg/kg s.c.) individually and in combination. Alone, neither ondansetron nor SDZ205-557 affected 5-HT-stimulated colonic transit, but when administered together, the drugs inhibited the stimulated transit by 88% (fig. 3). Furthermore, simultaneous administration of ondansetron (3.2 mg/kg p.o.) and the more potent and selective 5-HT₄ receptor antagonist
SB204070 (0.1–1.0 mg/kg, s.c.) also had a strong inhibitory effect (0.1 mg/kg, 112% inhibition; 1.0 mg/kg, 90% inhibition; fig. 4).

**Effect of 5-HT₄ receptor antagonist on 5-HT-induced diarrhea in mice.** The submaximal effective dose (0.32 mg/kg) of 5-HT was used to examine the effects of the test drugs on 5-HT-evoked diarrhea in mice, as reported previously.
(Kadowaki et al., 1993). The i.p. administration of 5-HT (0.32 mg/kg) induced diarrhea in more than 80% of fasted mice. Effects of the 5-HT3 receptor antagonists SDZ205-557 and SB204070 on 5-HT-induced diarrhea were tested. At low concentrations, neither SDZ205-557 (≤ 3.2 mg/kg s.c.; fig. 5) nor SB204070 (≤ 0.32 mg/kg s.c.; fig. 6) had an inhibitory effect on 5-HT-induced diarrhea. A reduction in the incidence of 5-HT-induced diarrhea was observed when a higher dose of SDZ205-557 (10 mg/kg s.c.; 33% decrease; fig. 5) or SB204070 (1.0 mg/kg s.c.; 38% decrease; fig. 6) was used.

**Effect of the combination of 5-HT3 receptor antagonist and 5-HT4 receptor antagonist on 5-HT-induced diarrhea in mice.** The observation that the combined antagonistic effects of 5-HT3 and 5-HT4 receptors were necessary to inhibit 5-HT-induced diarrhea prompted us to examine the role of these two 5-HT receptors in 5-HT-stimulated fluid secretion. First, the effect of the combined administration of ondansetron (3.2 mg/kg p.o.) and SB204070 (1.0 mg/kg s.c.) on 5-HT-evoked diarrhea was examined, because the same treatment almost completely abolished 5-HT-accelerated colonic transit in rats (fig. 4). A decrease in 5-HT-induced diarrhea was observed when either ondansetron (36% inhibition) or SB204070 (25% inhibition) was administered alone (fig. 7). The combined administration of ondansetron and SB204070 appeared to be additive, inhibiting 5-HT-induced diarrhea by 60% (fig. 7). However, in contrast to the colonic transit study, the combination of selective 5-HT3 and 5-HT4 receptor antagonists did not abolish the 5-HT-induced effect. To determine further the effects of combining 5-HT3 and 5-HT4 receptor antagonism, we tested the combination of a more potent 5-HT3 receptor antagonist, YM060 (0.032–0.32 mg/kg p.o.), and SB204070 (0.001–0.1 mg/kg s.c.). The administration of YM060 alone at 0.032 mg/kg was maximally effective at reducing the incidence of diarrhea (50% inhibition, fig. 8). The combined administration of SB204070 (0.01–0.1 mg/kg s.c.), which by itself had no effect, with YM060 resulted in a marked decrease in the incidence of 5-HT-induced diarrhea; complete inhibition of the 5-HT response was obtained when YM060 at 0.32 mg/kg p.o. was combined with SB204070 at 0.1 mg/kg s.c. (fig. 8).
Fig. 8. The effect of combined administration of YM060 and SB204070 on 5-HT-induced diarrhea in fasted mice. Animals were pretreated with the drugs or distilled water as a control 30 min before 5-HT injection (0.32 mg/kg i.p.), and the presence or absence of diarrhea was determined 15 min after the administration of 5-HT; n = 10 to 20 for each group. *P < .05, **P < .01 compared with the 5-HT-treated control group.

Discussion

In the present in vivo study, we have demonstrated that 5-HT accelerates colonic transit in rats and evokes diarrhea in mice through the activation of both 5-HT3 and 5-HT4 receptors. Both of these subtypes of 5-HT receptor have been located in the ENS (Craig and Clarke, 1990; Kilbinger and Wolf, 1992), and our observations therefore suggest that neural pathways involving both receptors mediate the actions of 5-HT in colonic motility and/or secretion.

Physiological studies have revealed that 5-HT is an important signaling molecule in the initiation of the peristaltic reflex (Bulbring and Lin, 1958; Bulbring and Crema, 1959a and b; Wade et al., 1996) and in the stimulation of secretory processes in the gut (Cooke and Reddix, 1994). Both 5-HT3 and 5-HT4 receptors mediate excitatory responses in enteric neurons (Wade et al., 1994; Pan and Galligan, 1994).

The 5-HT3 receptor is a ligand-gated cation-conducting channel (Derkach et al., 1989) that mediates a transient excitatory response to 5-HT (Vanner and Surprenant, 1990; Wade et al., 1994). This receptor has been reported to regulate an ascending excitatory reflex that can be elicited by mucosal stimulation in the small intestine (Neya et al., 1993; Yuan et al., 1994). The observation that administration of either 5-HT or the selective 5-HT3 agonist 2-methyl-5-HT enhances the colonic transit in conscious rats lends support to the idea that 5-HT3 receptors mediate the stimulation of GI motility; however, the discovery that neither ondansetron (pKi = 8.9 for 5-HT3 receptor, Akuzawa et al., 1995; pKi = 5.2 for 5-HT4 receptor; Miyata et al., 1995) nor granisetron (pKi = 9.5 for 5-HT3 receptor, Akuzawa et al., 1995; pKi = 5.6 for 5-HT4 receptor, Miyata et al., 1995), two potent and selective 5-HT3 receptor antagonists, was effective in blocking 5-HT-stimulated colonic transit indicates that other pathways besides those containing 5-HT3 receptors must exist (Kadowaki et al., 1993). These findings are consistent with other evidence that 5-HT3 receptor-selective ligands, 2-methyl-5-HT, tropisetron (in the 5-HT3-selective concentration range, 10^-9 to 10^-7 M) and granisetron, do not affect peristaltic responses (Buchheit and Buhl, 1991; Wade et al., 1996). Likewise, peristaltic contractions evoked in the isolated guinea pig ileum by the application of exogenous 5-HT are not blocked by a low concentration of tropisetron, nor are they inhibited by granisetron (Buchheit and Buhl, 1991) or ondansetron (Craig and Clarke, 1991).

Intracellular electrophysiological studies have revealed that 5-HT3 receptors presynaptically facilitate nicotinic synaptic transmission in the myenteric plexus of guinea pig ileum (Pan and Galligan, 1994). 5-HT4 receptor agonists have been reported to produce contractile responses in the guinea pig ascending and distal colon (Elswood et al., 1991; Kadowaki et al., 1992; Wardle and Sanger, 1993) and to accelerate colonic transit in conscious rats (Kadowaki et al., 1993). Furthermore, 5-HT-stimulated peristaltic reflexes in the guinea pig ileum are antagonized by the 5-HT4 receptor antagonist SDZ205-557 (Costall et al., 1993). These data are consistent with the idea that 5-HT3 receptors are, like 5-HT3 receptors, involved in enteric motor circuitry that is responsible for mediating the peristaltic reflex. In the present study, we tested the hypothesis that 5-HT3 receptors are involved in enteric motor functions in the colon by using the selective 5-HT4 receptor agonists SDZ205-557 (pA2 = 7.8 for 5-HT4 receptor, Wardle and Sanger, 1993; pKi = 6.9 for 5-HT4 receptor, Eglen et al., 1993) and SB204070 (pA2 = 10.7–11.1 for 5-HT4 receptor; pKi = 6.4–6.8 for 5-HT4 receptor; Wardle et al., 1994). Banner et al. (1993) reported that SDZ205-557 at a dose of 5 mg/kg produced the maximum inhibition of 5-HTP (10 mg/kg s.c.)-induced fecal pellet output in mice and that SB204070 inhibited the 5-HTP responses at doses of 0.003 to 1 mg/kg. Therefore, the doses 1 to 10 mg/kg of SDZ205-557 and 0.01 to 3.2 mg/kg of SB204070 were employed in the present study.

Neither SB204070 (0.01–1 mg/kg s.c.) nor SDZ205-557 (at doses up to 3.2 mg/kg s.c.) had an effect on 5-HT-induced colonic transit. However, at a high dose (10 mg/kg s.c.), SDZ205-557 reduced the 5-HT-stimulated colonic transit by 66%, an action that is likely to be due to the simultaneous antagonism of both 5-HT3 and 5-HT4 receptors, because neither the 5-HT3 receptor antagonist ondansetron nor the more potent and selective 5-HT4 receptor antagonist SB204070 significantly inhibited the 5-HT-stimulated transit. This interpretation is supported by recent studies in which a high dose (10 μmol/kg) of SDZ205-557 inhibited 5-HT3 receptor-mediated bradycardia response (Franks et al., 1995); furthermore, the selectivity of SDZ205-557 for 5-HT3 and 5-HT4 receptors has been demonstrated to be similar in rat, but not guinea pig (Eglen et al., 1993). Thus the high dose of SDZ205-557 that we employed probably affects both 5-HT3 and 5-HT4 receptors in rats. In our own study, FK1052, another 5-HT4 dual antagonist, greatly inhibited 5-HT-stimulated transit (Kadowaki et al., 1993). These data led us to propose that blockade of both 5-HT3 and 5-HT4 receptors, but not that of either receptor alone, may be required for inhibition of 5-HT stimulated colonic transit. We tested this hypothesis by the simultaneous administration of two drugs that have specific actions, namely the 5-HT3 receptor antagonist ondansetron and a 5-HT4 receptor antagonist (SDZ205-557 or SB204070). Administered alone, neither ondansetron nor a low dose (3.2 mg/kg s.c.) of SDZ205-557 inhibited the 5-HT-stimulated transit; however, when the drugs were given simultaneously, they slowed transit in a synergistic manner. Moreover, a similar result was obtained with ondansetron and SB204070.
These results are consistent with the idea that the effector pathways activated by 5-HT₃ and 5-HT₄ receptors interact in a cooperative manner to regulate colonic transit. 5-HT₃ receptors are located at cell bodies (Derkach et al., 1989; Wade et al., 1994), and 5-HT₄ receptors may be located at nerve endings of cholinergic interneurons because stimulation of 5-HT₄ receptors enhances nicotinic fast excitatory postsynaptic potentials in enteric neurons (Pan and Galligan, 1994). In addition, it has been shown that stimulation of both 5-HT₃ and 5-HT₄ receptors mediates a release of ACh in the guinea pig myenteric plexus (Kilbinger and Wolfe, 1992). These data suggest it is possible that 5-HT can stimulate colonic transit through the activation of either presynaptic 5-HT₄ receptors or postsynaptic 5-HT₃ receptors. The failure of selective antagonism of either 5-HT₃ or 5-HT₄ receptors to inhibit 5-HT-mediated responses suggests that the receptors are not arranged in series in the enteric microcircuit(s) critical to the response of the organ to exogenous 5-HT.

5-HT increases Iₑ in several species, such as rat (Bunce et al., 1991), guinea pig (Scott et al., 1992), pig (Hansen et al., 1994) and human (Borman and Burleigh, 1993; Kellum et al., 1994). Hypersecretion induced by cholera toxin (Beubler and Horina, 1990) and the diarrhea in patients with carcinoid syndrome (Gustafsen et al., 1986; Anderson et al., 1987; Platt et al., 1992) were partly reduced by 5-HT receptor antagonists. These findings strongly indicate that 5-HT is a potent secretagogue in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in most of the animals. Using this paradigm, we previously demonstrated (Kadowaki et al., 1993) that the diarrheal response evoked by 5-HT is only partly inhibited by the administration of 5-HT₃ antagonists such as ondansetron and granisetron; about 40% of the responding animals exhibited insensitivity to 5-HT₃ receptor antagonism. These results strongly indicate that 5-HT is a potent secretagogue in the gut. In the present study, the administration of 5-HT (0.32 mg/kg i.p.) to mice caused diarrhea in most of the animals. Using this paradigm, we previously demonstrated (Kadowaki et al., 1993) that the diarrheal response evoked by 5-HT is only partly inhibited by the administra-

5-HT-evoked diarrhea in mice was not achieved, even with the combination of 5-HT₃ and 5-HT₄ antagonists. This dose of ondansetron may be insufficient to block 5-HT₃ receptors completely, because ondansetron is less effective in blocking some 5-HT₃-mediated responses than other 5-HT₃ receptor antagonists (Miyata et al., 1992). Thus a more detailed dose-response relationship for the inhibition of 5-HT-evoked diarrhea was investigated, using the more potent 5-HT₃ receptor antagonist YM060 (pKᵢ = 11.5 for 5-HT₃ receptor, Akuzawa et al., 1995; pKᵢ = 5.5 for 5-HT₄ receptor, Miyata et al., 1995) together with SB204070. The maximum effect of YM060 alone was a 50% inhibition of 5-HT-induced diarrhea, an effect that was observed at a dose of 0.032 mg/kg; further increases of the dose to 0.1 or 0.32 mg/kg caused no further inhibition. These results were consistent with our previous findings (Kadowaki et al., 1993) in which other 5-HT₃ receptor antagonists were used. Again, the combination of the specific blockade of 5-HT₃ receptors by YM060, with 5-HT₄ specific doses of SB204070 (0.01–0.1 mg/kg s.c.) resulted in the dose-dependent inhibition of 5-HT-induced diarrhea although neither compound alone had an inhibitory effect. A complete inhibition of 5-HT-induced diarrhea was obtained when the antagonists were combined at doses of 0.32 mg/kg YM060 and 0.1 mg/kg SB204070. These results suggest that 5-HT stimulates fluid secretion by a mechanism that involves both 5-HT₃ and 5-HT₄ receptors and that when either 5-HT₃ or 5-HT₄ receptors are selectively blocked, exogenous 5-HT induces diarrhea via activation of the alternative receptor.

Recently, Sidhu and Cooke (1995) showed that an increase in Iₑ evoked by mucosal stroking of guinea pig distal colon is mediated by activation of 5-HT₁P receptor. Furthermore, Wade et al., (1996) has shown that peristaltic reflex in guinea pig distal colon is inhibited by the 5-HT₁P receptor antagonist 5-HTP-DP. Therefore, it remains to be investigated whether there is an interaction between 5-HT₁P receptor and 5-HT₃ and/or 5-HT₄ receptor.

Taken together, these results indicate that 5-HT accelerates colonic transit in rats and evokes diarrhea in mice by the combined activation of both 5-HT₃ and 5-HT₄ receptors. These receptors must be located in separate—probably parallel—pathways, because the complete blockade of either receptor alone is insufficient to abolish the 5-HT-induced effect. Furthermore, the present results suggest that a drug that
has mixed 5-HT₃ and 5-HT₄ antagonist properties may be a more effective agent in the treatment of functional colonic disorders (e.g., irritable bowel syndrome) than one that acts as a highly selective blocker of either receptor alone.

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References


