AGONIST AND ANTAGONIST ACTIONS OF MORPHINE-LIKE DRUGS ON THE GUINEA-PIG ISOLATED ILEUM

BY

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Substitution of the side-chain attached to the $N$ atom of narcotic analgesic drugs of the morphine, morphinan and benzomorphan series leads to compounds which antagonize the action of the parent compounds; nalorphine and levallorphan, the allyl analogues of morphine and levorphanol, are widely used as "narcotic antagonists." However, these and other analogues also exhibit agonist properties; for example, they may act as analgesics and depress respiration (Eddy, Halbach & Braenden, 1957; Lasagna, De Kornfeld & Pearson, 1964).

This dual action of the "narcotic antagonists" has also been observed in isolated tissues. Paton (1957a) showed that morphine and nalorphine are equally effective in depressing the electrically induced contraction of the longitudinal muscle of the guinea-pig ileum, and Gyang, Kosterlitz & Lees (1964) found that the same holds for their inhibitory actions on the peristaltic reflex or the graded reflex contraction of the longitudinal muscle. The experiments presented in this paper were planned to analyse more fully the actions of "narcotic agonists" and "narcotic antagonists" on the guinea-pig ileum.

METHODS

Experimental procedure. All experiments were performed on the guinea-pig isolated ileum; the terminal portion was used after discarding the 10 cm nearest to the ileo-caecal junction.

In the first set of experiments, the depressant action of morphine-like drugs was tested on the contraction of the longitudinal muscle induced by coaxial electrical stimulation (Paton, 1955). The bath fluid, Krebs solution (40 ml.) to which hexamethonium bromide (0.069 mM) and mepyramine maleate (0.125 mM) were added, was bubbled with 95% oxygen and 5% carbon dioxide. The temperature was 36°C. The stimuli were 1.5 times maximal rectangular pulses of 0.5 to 1 msec duration, at a frequency of 6 to 7/min. The twitch-like contractions were recorded by means of a pendulum lever (Paton, 1957b). The ileum was exposed to the morphine-like drugs for 1 to 3 min, until inhibition was maximal. The results were plotted as the percentage by which the size of the control twitch was reduced against the concentration of the drug.

In the second set of experiments, the peristaltic reflex, recorded by the method of Trendelenburg (1917), was used to study the depressant action of morphine-like drugs. Since the peristaltic reflex is practically an all-or-none response to distension of the lumen of the ileum, the results cannot be interpreted quantitatively.

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In a third set of experiments, the graded reflex contraction of the longitudinal muscle was elicited by distension of the lumen to varying degrees, the contractions of the circular muscle being prevented by hexamethonium (0.069 mM). The shortening of the isotonically contracting muscle was plotted against the volume of fluid distending the lumen (Gyang et al., 1964).

Drugs. The "narcotic agonists" used were: morphine hydrochloride, levorphanol (N-allylnormorphine) hydrochloride, N-methylallylnormorphine hydrochloride, levallorphan (N-allylnormorphine) tartrate and phenazocine (2'-hydroxy-2-cyclopropylmethyl-5,9-dimethyl-6,7-benzomorphan) hydrochloride. The following "narcotic antagonists" were used: nalorphine (N-allylnormorphine) hydrochloride, N-methylallylnormorphine hydrochloride, levallorphan (N-allylnormorphine) tartrate, cyclazocine (2'-hydroxy-2-cyclopropylmethyl-5,9-dimethyl-6,7-benzomorphan), pentazocine (2'-hydroxy-2-(3,3-dimethylallyl)-5,9-dimethyl-6,7-benzomorphan) and SK & F 10047 (2'-hydroxy-2-allyl-5,9-dimethyl-6,7-benzomorphan). The benzomorphan bases were dissolved in the required amount of HCl; phenazocine was available as the hydrochloride.

Other drugs used were: hexamethonium bromide, phenoxybenzamine hydrochloride, propranolol hydrochloride, noradrenaline bitartrate monohydrate and acetylcholine chloride.

The concentrations of all drugs are expressed as mM, μM or nM (10^-6 M).

RESULTS

Transmural stimulation of ileal longitudinal muscle

Agonist action of morphine-like drugs

Morphine. When Paton (1957a) made his observations on the depressant action of morphine-like drugs, he showed that the assessment of their potencies was difficult because tachyphylaxis developed readily. He found that it was important to use only small doses of the drugs and expose the gut to the drugs at intervals of not less than 30 min. We have re-examined the conditions necessary to obtain dose-response curves and found that (1) the interval between doses had to be not less than 15 to 20 min, (2) morphine must not be left in the bath for longer than 3 min and (3) the dose which inhibited the twitch response by 80 to 90% must not be exceeded. In the experiment shown in Fig. 1 the depressant actions of two concentrations of morphine (16 and 132 nM) remained constant for 6 hr, although in the later stages, from about 4 hr onwards, the height of the twitch tended to recover somewhat in the presence of morphine. Dose-response curves were reproducible for at least 4 to 5 hr (Fig. 2); a 50% inhibition was usually obtained with a concentration of 90 to 120 nM.

![Fig. 1. Inhibitory effect of repeated exposures to morphine on twitch of longitudinal muscle induced by supramaximal coaxial stimulation (six stimuli/min). Two concentrations of morphine, 16 and 132 nM, were tested alternately at intervals of 20 min: (a) at 1½ hr (first exposure); (b) at 3½ hr; (c) at 5½ hr; (d) at 7½ hr after setting up the preparation.](image-url)
In some preparations the interval between doses could be reduced to 5 min without tachyphylaxis occurring, but with intervals of 20 min more reliable results were obtained. It was important to avoid large doses since tachyphylaxis developed rapidly, even with intervals of 20 min between doses.

**Nalorphine.** The depressant action of this N-allyl analogue of morphine was found to be of the same order as morphine (Fig. 3,a). However, tachyphylaxis developed much more rapidly with nalorphine than with morphine; when dose-response curves were repeated over a period of several hours they were gradually displaced towards the right (Fig. 3,b).
N-methylallylnormorphine. This compound was much less potent in depressing the contraction of the longitudinal muscle than either morphine or nalorphine. It inhibited the twitch by 10 to 20% over a wide range of concentrations (0.5 to 20 μM) (Fig. 4). A 50% inhibition was obtained with a concentration of 100 μM; however, since concentrations greater than 60 μM had an anti-acetylcholine effect, the morphine-like action of N-methylallylnormorphine was probably even smaller than that calculated from the ratio of concentrations causing the same degree of inhibition. In a concentration of 130 μM, N-allylnormorphine halved the size of the contraction induced by 17 nM acetylcholine.

Levorphanol and levallorphan. Levorphanol was about three to four times more potent than morphine in depressing the twitch due to coaxial stimulation, 15 to 20 nM levorphanol producing a 50% inhibition (Fig. 5). When the drug was added at intervals of 20 min, tachyphylaxis was negligible. The onset of, and recovery from, inhibition was slower with levorphanol than with morphine.
Fig. 6. Inhibitory effects of phenazocine and cyclazocine on twitch of longitudinal muscle induced by coaxial stimulation. Dose-response curves were obtained with 20-min intervals between doses: (a) curves for phenazocine obtained in the following order: *, V, △, □. (b) Curves for cyclazocine: ○, Δ, □, V. Abscissa: concentrations (nM) of phenazocine or cyclazocine; ordinate: inhibition of twitch.

The allyl analogue of levorphanol, levallorphan, on first addition to the organ bath was even more potent than its parent substance, but tachyphylaxis developed very rapidly (Fig. 5).

*Phenazocine, cyclazocine, pentazocine and SK and F 10047.* It was difficult to construct dose-response curves for any of the benzomorphan derivatives since tachyphylaxis developed rapidly (Fig. 6). Their initial potencies were approximately as follows: a 30% inhibition of the twitch was obtained with 3 to 4 nM phenazocine (Fig. 6,a), 2.5 nM cyclazocine (Fig. 6,b), 140 nM pentazocine and 38 nM SK and F (10047, while the equi-active concentration of morphine was 33 nM (Fig. 2). When the concentration of pentazocine was raised to 700 nM, an anti-acetylcholine action was seen.

These observations led to the conclusion that there are “narcotic antagonists” which are able to depress the twitch of the longitudinal muscle as effectively as their related “narcotic agonists.” For example, nalorphine is as potent as morphine, levallorphan is more potent than levorphanol and cyclazocine is at least as potent as phenazocine. There were differences in the rate of onset of action of the individual drugs. However, the “agonists” as a group did not act more rapidly than the “antagonists”; the maximum depressant effects were obtained with morphine in 1 to 1.5 min, with nalorphine in 1.5 to 2 min, with levorphanol in 2 to 3 min and with phenazocine in 3 to 4 min.

*Antagonist action of morphine-like drugs*  
The fact that tachyphylaxis developed with all compounds tested was a strong indication that they would exhibit antagonist action under suitable conditions. While the N-allyl analogues used as “antagonists” in clinical practice—e.g., nalorphine and levallorphan—had at least as much agonist activity as the corresponding N-methyl compounds, tachyphylaxis developed more rapidly than with the “agonists.” Because of the agonist activity of the “antagonists,” the conventional methods of testing for antagonism did not yield decisive results.

In view of these difficulties, the drugs were tested for antagonism as follows. Use was made of the observation that a dose of morphine which depressed the twitch by 60 to
90% could be added to the bath fluid at 20-min intervals for several hr without producing tachyphylaxis. The compound whose antagonist activity was to be investigated was added to the bath fluid in a low concentration which, by itself, reduced the twitch height by only 10 to 20%, and was left in the bath for 1 hr. The first test dose of morphine was applied 2 to 3 min after addition of the antagonist compound; the inhibitory effect of morphine was tested at 20-min intervals for 1 hr, after which the antagonist compound was washed out (Fig. 7). The small inhibitory effect of the antagonist compound decreased a little during the first 5 min of exposure and then remained constant.

![Fig. 7. Antagonism by low concentration of morphine of inhibitory effect of morphine on twitch of longitudinal muscle induced by coaxial stimulation. The upper panel shows the inhibitory effects of the test concentration of morphine (132 nM) and of the low concentration (33 nM) plus the test concentration (132 nM). The lower panel shows the effect of the continuing presence of the low concentration (33 nM) on the inhibitory effect of the test concentration. The low concentration was present between the arrows.](image)

Two compounds were tested in any one experiment. In this way it was shown that morphine had a weak antagonist action and that nalorphine was more effective as an antagonist (Fig. 8). This experiment also showed that a single application of a mixture of 15 nM nalorphine and 132 nM morphine had an inhibitory effect which was only slightly less than that of 132 nM morphine. However, when the ileum had been exposed to nalorphine for 2 to 3 min, the antagonist effect of nalorphine increased and reached its maximum 20 min later. The antagonist effect of morphine developed more slowly and recovery was more rapid than from the antagonist effects of nalorphine and N-methylallylnormorphine (Figs. 8 and 9).

Although N-methylallylnormorphine is a very weak agonist, surprisingly low concentrations (260 nM) could be used to test its antagonist action, because of the shallow slope of the lower part of the dose-response curve (Fig. 4). The antagonist activity of N-methylallylnormorphine (Fig. 9) seemed to be of the same order as that of nalorphine.

The antagonist action of levorphanol was greater than that of morphine, the inhibitory effect of the test dose of morphine (132 nM) being reduced in the presence of levorphanol (3 nM) from 87 to 50%; however, the presence of levallorphan (3 nM) reduced the
Fig. 8. Antagonism by low concentrations of morphine or nalorphine of inhibitory effect of morphine on twitch of longitudinal muscle induced by coaxial stimulation. The inhibitory effect of morphine (132 nM) before, in the presence of, and after exposure to a low concentration of morphine (16 nM), ●, or nalorphine (15 nM), ○, in this order. The inhibitory effects of single applications of: morphine (16 nM), △; nalorphine (15 nM), ▽; morphine (132 nM) plus morphine (16 nM), ■; or morphine (132 nM) plus nalorphine (15 nM), □. Abscissa: time (min); ordinate: inhibition of twitch.

Fig. 9. Antagonism by low concentrations of morphine or N-methylallylnormorphine of inhibitory effect of morphine on twitch of longitudinal muscle induced by coaxial stimulation. The inhibitory effect of morphine (132 nM) before, in the presence of, and after exposure to a low concentration of morphine (16 nM), ●, or N-methylallylnormorphine (260 nM), ○, in this order. The inhibitory effect of single applications of: morphine (16 nM), △; N-methylallylnormorphine (260 nM), ◻; morphine (132 nM) plus morphine (16 nM), ■; morphine (132 nM) plus N-methylallylnormorphine (260 nM), □. Abscissa: time (min); ordinate: inhibition of twitch.

Inhibitory effect of the test dose of morphine from 87 to 22%. After washing out levorphanol the depressant effect of morphine was completely restored in 40 min, while the recovery after washing out levallophan was still incomplete after 60 min, the inhibitory effect of morphine being then only 45% of its original value. In another experiment, levorphanol was compared directly with morphine; levorphanol (3.5 nM) reduced the inhibitory effect of the test dose of morphine from 95 to 70%, while the corresponding reduction by morphine (16 nM) was from 92 to 82%.
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Of the benzomorphan derivatives, the "antagonist," cyclazocine (2 nM), reduced the inhibitory effect of the test dose of morphine from 65 to 30%, while the "agonist," phenazocine (1.5 nM), reduced it from 62 to 45%. The recovery after cyclazocine was slower than after phenazocine.

In order to gain some information about the time which is required for the development of, and recovery from, tachyphylaxis, the effects of doses of morphine added to the bath at intervals of 5 min and left for 90 sec were compared with the effects of doses of nalorphine or N-methylallylnormorphine. If morphine (132 nM) was added in this way, there was a small initial reduction of its inhibitory effect, which then remained constant during the course of 1 hr, while the inhibitory effect of doses of nalorphine (120 nM) added in a similar manner was reduced from 52 to 33%; when, at the end of the series of additions of nalorphine, morphine was tested again, its inhibitory action was depressed and recovered slowly over a period of 20 min (Fig. 10). When morphine (132 nM) and N-methylallylnormorphine (650 nM) were compared in a similar manner, the inhibitory effect of morphine remained unchanged while that of N-methylallylnormorphine diminished to less than half its original value; recovery of the inhibitory effect of morphine, added after the last dose of N-methylallylnormorphine, was very slow.

![Fig. 10. Tachyphylactic effects of repeated applications of morphine or nalorphine. Inhibition of twitch of longitudinal muscle induced by coaxial stimulation; 5-min intervals between doses, repeated for 1 hr: morphine (132 nM), ○; followed after an interval of 30 min by nalorphine (120 nM), □; followed immediately by morphine (132 nM), △. Abscissa: time (min); ordinate inhibition of twitch.](image)

Peristaltic reflex

Gyang et al. (1964) reported that, when used as an agonist, nalorphine had approximately the same inhibitory action on the peristaltic reflex as morphine. However, after nalorphine had been left in the bath for 10 to 15 min, the reflex could be elicited again and was then resistant to the inhibitory action of morphine and other narcotic analgesics.

Further analysis showed that, as was found for the contraction of the longitudinal muscle induced by coaxial stimulation, morphine and nalorphine have both agonist and antagonist effects on the peristaltic reflex, the antagonist effect being more pronounced with nalorphine than with morphine. With low concentrations of morphine (33 nM),
Fig. 11. Effect of morphine on peristaltic reflex. In each panel: upper tracing, contraction of the longitudinal muscle, shortening upwards; lower tracing, filling of the intestinal lumen, increase downwards. The numbers below the tracings refer to filling pressures (cm H₂O). Top row: (a) controls; (b) 3 to 9 min after addition of morphine (33 nM). Middle row: (a) 15 to 21 min and (b) 30 to 36 min after addition of morphine (33 nM). Bottom row: (a) 3 to 9 min and (b) 60 to 66 min after addition of morphine (132 nM).

Fig. 12. Effect of nalorphine on peristaltic reflex. Tracings as in Fig. 11. Top row: (a) controls; (b) 3 to 9 min and (c) 15 to 21 min after addition of nalorphine (15 nM). Bottom row: (a) 3 to 9 min and (b) 60 to 66 min after addition of nalorphine (120 nM); (c) 60 min after washing out nalorphine.
inhibition of the reflex was transient but with higher concentrations (132 nM) inhibition remained unchanged for 1 hr (Fig. 11). Similarly, with low concentrations of nalorphine (15 nM), the inhibitory action was weak and short-lasting, while with higher concentrations (120 nM) the inhibitory action persisted for 1 hr (Fig. 12). The observation that the inhibitory action of a low concentration of nalorphine (15 nM) is transient is the basis of the use of this drug as an antagonist to the inhibitory action of morphine-like compounds. For example, Gyang et al. (1964) showed that the inhibitory action of morphine or similar substances is abolished after exposure of the ileum to 15 nM nalorphine for 15 min. By treating the ileum with a low concentration of morphine (15 nM), a weak antagonist action against a higher concentration of morphine (132 nM) can be demonstrated.

N-methylallylnormorphine in a relatively high concentration (3.3 μM) had only a transient inhibitory action on the peristaltic reflex but in higher concentrations (6.6 μM) this action remained unchanged for 1 hr. After exposure of the ileum to a low concentration of N-methylallylnormorphine (210 nM) for 15 min, the peristaltic reflex was no longer depressed by morphine (132 nM); this antagonist effect of N-methylallylnormorphine was reversed by washing out the drug.

Similarly, phenazocine, pentazocine, cyclazocine and SK and F 10047 exhibited both agonist and antagonist activities. For example, cyclazocine in a concentration of 9 nM inhibited the peristaltic reflex; on the other hand, when cyclazocine (2.3 nM) was applied to ileum in which the peristaltic reflex had been inhibited by morphine (132 nM), this inhibition was reversed as long as the cyclazocine remained in the organ bath (Fig. 13).

![Fig. 13. Antagonism by cyclazocine of inhibitory effect of morphine on peristaltic reflex. Tracings as in Fig. 11. (a) Controls; (b) 15 to 21 min after addition of morphine (132 nM), morphine being left in the bath throughout the experiment; (c) 3 to 9 min and (d) 15 to 21 min after the addition of cyclazocine (2.3 nM); (e) 15 to 21 min after washing out cyclazocine.](image)

**Graded reflex contraction of longitudinal muscle**

In the presence of ganglion-blocking agents such as hexamethonium, increasing the distension of the lumen causes a graded contraction of the longitudinal muscle (Gyang et al., 1964). This reflex contraction is depressed by morphine, nalorphine, N-methylallylnormorphine, phenazocine, pentazocine or cyclazocine. The concentrations of the drugs were of the same order as required to inhibit the peristaltic reflex. Antagonism of the depressant effect of morphine is caused by lower concentrations of the drugs, viz., nalorphine (15 nM), N-methylallylnormorphine (260 nM), pentazocine (175 nM) or cyclazocine (2.3 nM).
Fig. 14. Effects of adrenergic blocking drugs on inhibition by morphine or noradrenaline of twitch of longitudinal muscle induced by coaxial stimulation. Dose-response curves for the two drugs applied alternately at intervals of 10 min. Controls: morphine, ●; noradrenaline, ○. After addition of phenoxybenzamine (15 nm) and propranolol (850 nm): during first hr, morphine, △; noradrenaline, △; during second hr, morphine, ▽; noradrenaline, ▽; during third hr, morphine, ■; noradrenaline, □. Abscissa: concentrations of morphine or noradrenaline (nm); ordinate: inhibition of twitch.

**Effect of adrenergic blocking agents**

Schaumann (1958) put forward the hypothesis that the depressant action of morphine on the contraction of the longitudinal muscle evoked by coaxial electrical stimulation might be due to a release of catecholamines. This hypothesis was tested by examining the effect of the α blocking agent, phenoxybenzamine, and the β blocking agent, propranolol, on the depression of the twitch caused by noradrenaline or morphine. While the inhibitory effect of adrenaline or noradrenaline was readily antagonized by the two blocking drugs, the inhibitory effect of morphine remained unaffected (Fig. 14). There is therefore no reason to believe that morphine acts by releasing catecholamines.

**DISCUSSION**

The purpose of this investigation was to distinguish between the agonist and antagonist actions of representatives of the morphine, morphinan and benzomorphan groups of compounds. The test object was the guinea-pig isolated ileum, in which three responses were examined: the peristaltic reflex elicited by distension of the lumen; the graded reflex contraction of the longitudinal muscle elicited in the same way; and the contraction of the longitudinal muscle evoked by transmural electrical stimulation. The results obtained with the three methods indicated that all compounds exhibited agonist and antagonist activities.

Approximate values found for the inhibitory actions of the drugs on the peristaltic reflex and the transmurally stimulated ileum, together with data on their analgesic potencies
in man, are shown in Table 1. There is a fairly good correlation between the analgesic potencies and the potencies as inhibitors in the guinea-pig ileum. This correlation holds for both “narcotic agonists” and “narcotic antagonists,” although there is some discrepancy with cyclazocine, the analgesic potency of which as given by Lasagna et al. (1964) is surprisingly high.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analgesic potency in man (morphine=1)</th>
<th>Agonist activity</th>
<th>Antagonist activity</th>
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<td>Concentration inhibiting peristaltic reflex for 60 min (nM)</td>
<td>Dose ratio for inhibition of peristaltic response to coacXial stimulation (morphine=1)</td>
<td>Reduction by small doses of drug of inhibition produced by test dose of morphine %</td>
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When tested for antagonist activity in the guinea-pig ileum, all drugs exhibit such activity irrespective of whether they are classed clinically as “narcotic agonists” or “narcotic antagonists,” the latter, however, being stronger antagonists that the former: nalorphine and N-methylallylnormorphine are more potent antagonists than morphine, levallophan is more potent than levorphanol, and cyclazocine and pentazocine exhibit more antagonist activity than phenazocine. When morphine, levorphanol and phenazocine are compared, morphine shows the smallest antagonist activity (Table 1).

The time-courses of the onset of the agonist and antagonist actions are quite different. The agonist effect begins immediately after adding the drug to the organ bath and is usually complete after about 90 sec, with minor differences for individual drugs. On the other hand, the antagonist effect develops slowly, being at its maximum after 15 to 30 min. Similarly, recovery from the agonist action is rapid after washing out the drug, while recovery from the antagonist action may not be complete 1 hr after washing out the drug.

It seems to be an important observation that recovery from the antagonist action of the “narcotic agonists,” morphine, levorphanol and phenazocine, is more rapid than the recovery from the antagonist action of the corresponding “narcotic antagonists,” nalorphine, N-methylallylnormorphine, levallophan and cyclazocine. While both groups of drugs are partial agonists, the “narcotic antagonists” appear to form a longer-lasting combination with the receptors.
When the "narcotic antagonists" are to be used as antagonists, in order to reduce their agonist activity concentrations have to be chosen which are so low that they produce an inhibition of not more than 10 to 20% of the twitch of the longitudinal muscle. In higher concentrations the agonist activity of these compounds becomes so prominent that the antagonist activity is completely masked; for instance, the peristaltic reflex remains inhibited for 1 hr or more. Optimal concentrations are 10 to 15 nM nalorphine, 2 to 4 nM levallorphan and 1 to 3 nM cyclazocine. Because of the weak agonist activity of \( N \)-methylallylnormorphine, this drug can be used in a wide range of concentrations (0.5 to 10 \( \mu M \)). A similar relationship between agonist and antagonist activity has been observed in experiments on analgesia in man, where low concentrations of nalorphine reduce the effect of morphine while higher concentrations exert an analgesic effect of their own (Houde & Wallenstein, 1956).

It is tempting to associate the development of tachyphylaxis to "narcotic agonists" and "narcotic antagonists" in the guinea-pig ileum with the tolerance and physical dependence which are caused in man, not only by "narcotic agonists" but also by such "narcotic antagonists" as cyclazocine and nalorphine (Martin, Fraser, Gorodetzky & Rosenberg, 1965; Martin & Gorodetzky, 1965). Nevertheless, none of the findings obtained on the ileum is suitable for predicting whether or not a drug is liable to produce psychical dependence and thus cause addiction (Eddy, Halbach, Isbell & Seever, 1965).

**SUMMARY**

1. Compounds of the morphine, morphinan and benzomorphan series were examined for agonist and antagonist actions on the guinea-pig isolated ileum. Their actions were tested on three responses: the inhibition of (1) the twitch of the longitudinal muscle evoked by transmural stimulation, (2) the peristaltic reflex, (3) the graded reflex contraction of the longitudinal muscle elicited by distension of the lumen.

2. All compounds, "narcotic agonists" (morphine, levorphanol or phenazocine) or "narcotic antagonists" (nalorphine, \( N \)-methylallylnormorphine, levallorphan, cyclazocine, pentazocine) showed agonist and antagonist activities. The agonist activities were closely correlated with the analgesic potencies in man. The "narcotic antagonists" showed more antagonist activity than the "narcotic agonists."

3. The agonist action of "narcotic agonists" or "narcotic antagonists" has a rapid onset and is readily reversible. The antagonist action develops more slowly; it is much less readily reversed in "narcotic antagonists" than in "narcotic agonists."

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REFERENCES


