Comparative study on the effect of neostigmine, trimetaphan and oxyphenonium on some aspects of 5-hydroxytryptamine metabolism in rats

Since a relation between peristalsis and intestinal 5-hydroxytryptamine (5-HT) content has been demonstrated by Bülbring & Crema (1959), the effect that three compounds, which affect intestinal motility and peristalsis have on the 5-HT content of the intestine and 5-hydroxyindoleacetic acid (5-HIAA) urinary excretion has been investigated. The drugs were neostigmine, trimetaphan (a competitive ganglion blocker) and oxyphenonium (a parasympathetic depressant).

Adult male rats, 120–150 g, were divided into groups of 8 animals. The drugs were injected intramuscularly in doses of 50 μg kg^{-1} for neostigmine, 0·5 mg kg^{-1} for oxyphenonium and 50 mg kg^{-1} intraperitoneally for trimetaphan either acutely, as a single injection, or chronically, as daily injections for 7 and 14 days. For the determination of 5-HT content in the intestine, a control group was used for each drug-treated group, and received normal saline in the same dose as the respective drug. At each of the time intervals, one drug-treated group and one control group were decapitated 2 h after the last injection. 5-HT was extracted from the small intestine by the method of Amin, Crawford & Gaddum (1954) and evaluated using the 4-point assay method on the rat uterus. This method is sensitive to one ng 5-HT and its specificity was tested at the end of the assay by methysergide.

For the determination of urinary 5-HIAA, the acute and chronic effects of the drugs was determined in other groups of 8 male rats kept in pairs in 4 separate metabolic cages. Only one group of 8 rats was used as controls for each drug throughout the experimental period. Urine was collected 24 h after the last injection and analysed for 5-HIAA by the method of MacFarlane, Dalgliesh & others (1957) as modified by Abdel Aziz (1969).

The effects of the different drugs and treatments on both the intestinal 5-HT and urinary output of 5-HIAA are summarized in Tables 1 and 2 respectively.

Neostigmine produced a significant decrease of the intestinal 5-HT content with a significant increase in the 5-HIAA urinary output. Such an effect may have been due to an increase in the release of 5-HT content from the intestine. Neostigmine potentiates the effects of acetylcholine (Wilson, 1955), which may possibly act to

Table 1. *Effect of various drugs on the 5-HT content (μg^{-1} g wet tissue) of the small intestine of male albino rats 2 h after different courses of administration.* Each value represents the mean of 8 animals (±s.e.). Percentage change refers to changes of treated group from concurrent control group.

Treatment	Single dose	One week	Two weeks
Neostigmine (50 μg kg^{-1}, i.m.)	1·16 ± 0·04	*0·73 ± 0·11	*0·38 ± 0·02
Control	1·27 ± 0·14	1·10 ± 0·11	0·68 ± 0·08
Percentage change	−7	−33·6	−44·1
Oxyphenonium (0·5 mg kg^{-1}, i.m.)	*2·10 ± 0·28	*2·91 ± 0·30	*1·80 ± 0·19
Control	1·41 ± 0·11	1·40 ± 0·13	1·12 ± 0·13
Percentage change	+49	+108	+60·7
Trimetaphan (50 mg kg^{-1}, i.p.)	*0·67 ± 0·07*	0·95 ± 0·11	0·62 ± 0·06
Control	1·41 ± 0·11	1·10 ± 0·11	0·68 ± 0·08
Percentage change	−52·4	−13·6	−8·8

* Significant difference from the corresponding control ($P < 0·05$).

Table 2. *Effect of various drugs on the 24 h urinary output of 5-HIAA* ($\mu g\ rat^{-1}\ 24\ h^{-1}$) *of male albino rats, after different courses of administration.* Each value is the mean of 8 animals (4 samples) ± s.e. Only one group of control animals were used for each treatment.

Treatment	Control	Single dose	One week	Two weeks
Neostigmine (50 $\mu g\ kg^{-1}$, i.m.)	26·4 ± 1·80	39·0 ± 1·89*	38·3 ± 0·96*	36·7 ± 1·41*
Percentage change from control		+47·4	+45	+39
Oxyphenonium (0·5 mg kg^{-1}, i.m.)	24·4 ± 0·96	14·0 ± 0·45*	13·1 ± 0·24*	16·3 ± 0·77*
Percentage change from control		−42·6	−46·3	−33·2
Trimetaphan (50 mg kg^{-1}, i.p.)	33·2 ± 1·14	24·1 ± 0·47*	30·7 ± 1·05	32·1 ± 0·98
Percentage change from control		−27·4	−7·5	−3·3

* Significant difference from the corresponding control ($P < 0.05$).

release 5-HT from the entero chromaffin cells of the intestine (Thompson, Spezia & Angulo, 1969). It also leads to an increase in tone of the gastrointestinal tract (Aliev, 1958) and this is accompanied by an increase in 5-HT release (Paton & Vane, 1963). The increased release of 5-HT could lead to a high rate of urinary 5-HIAA excretion (Vaisfeld & Kolmenskaya, 1965) as we observed. The results after treatment with oxyphenonium showed a reverse picture of that of neostigimine. The effect may have been due to a decreased release of intestinal 5-HT or to the enhancement of the rate of biosynthesis. Had the release of the amine been increased, the concentration of its metabolite would also have been increased. However, this was not so, the urinary 5-HIAA level was decreased. The decreased release of the 5-HT may have been due to the parasympathetic depressant action of the drug (Schapiro, Wruble & others, 1968) which results in inhibition of intestinal motility (Tucker, 1965) and thus a reduction in the release of 5-HT. However, oxyphenonium was reported to increase the pH of the gastric and duodenal secretions (Lasus & Lages, 1965), an effect which is known to lead to an increase in 5-HT tissue content. Trimetaphan, induced a decrease in intestinal 5-HT content together with a decrease of 5-HIAA urinary output. Continuation of drug treatment resulted in the return of the tissue amine content and its urinary metabolite back to normal values. The reduced level of 5-HT in the intestine was possibly a result of a decrease in the rate of biosynthesis of the amine; an effect which is liable to tolerance with chronic drug administration.

The above results lend further support to the suggestion that the parasympathetic nerve supply to the intestine and the release of 5-HT therein are intimately interrelated and involved in modulating intestinal peristalsis.

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Caesium ion: antagonism to chlorpromazine- and L-dopa-produced behavioural depression in mice

The efficacy of lithium salts in the treatment of manic-depressive illness (Cade, 1949) has stimulated interest in the effects of other alkali metal ions on behaviour. An antidepressant effect of rubidium salts has been suggested (Fieve, Meltzer & others, 1973). Similarities in the pharmacological effects of rubidium and caesium (Cs) salts have prompted the pre-clinical evaluation of Cs^+ as an antidepressant (Eichelman, Thoa & Perez-Cruet, 1973; Messiha & Krantz, 1973). The present study utilized the drug-induced depression in motility produced by chlorpromazine or L-dopa in mice as an experimental model to determine whether Cs^+ might have antidepressant properties.

Male Swiss albino, Sprague-Dawley mice, 8–12 weeks old, were caged in groups of six at 23–26° and had free access to Purina lab chow and water for at least two weeks before experiments. An intraperitoneal injection of CsCl (2·5 m equiv kg^{-1} day^{-1}) was administered for 5 consecutive days followed by a 48 h drug-free period before chlorpromazine (2·0 mg kg^{-1}, i.p.) or L-dopa-methylester (500·0 mg kg^{-1}, i.p.) dissolved in saline. Control injections were of isotonic saline. Injection volumes did not exceed 0·3 ml. Food was withheld for 24 h before administration of chlorpromazine, L-dopa or the control saline injection.

Spontaneous locomotor activity was measured in groups of three mice by means of a selective activity meter device (Columbus Instruments) adapted to the home cages and recorded at 10 min intervals on a digital counter beginning 10 min after administration of chlorpromazine, L-dopa or the control injection. Control and experimental groups were tested at the same time at room temperature. The statistical significance of the results was analysed by two-tailed *t*-test for independent means.

Fig. 1 shows the effects produced by short-term pretreatment with CsCl on chlorpromazine and L-dopa-mediated decrease of spontaneous locomotor activity in mice, as a function of time. Administration of chlorpromazine or L-dopa markedly decreased spontaneous locomotor activity from saline controls. Conversely, CsCl pretreatment significantly increased motility during the 40–60 min period of testing (mid panel). In general, treatment with CsCl before chlorpromazine significantly counteracted the chlorpromazine-induced decline in mice motility during the 60 min period of testing (left panel). For example administration of chloropromazine to Cs-pretreated mice resulted in mean square root motor activity counts of $16{\cdot}3 \pm 1{\cdot}7$ greater than $9{\cdot}4 \pm 1{\cdot}2$ counts obtained for the corresponding controls ($P < 0{\cdot}01$) at 20 min of the observation period. Administration of L-dopa to Cs-pretreated mice produced 34·8 and 27·7% increased motility from controls at 30 min and 60 min, respectively (right panel). However, this increase was not statistically significant. The results show that CsCl administration both increased spontaneous locomotor activity in mice and counteracted the chlorpromazine-induced decline in mice motility, while the effect of CsCl on the L-dopa-induced decrease in mice motility was less pro-