tration values for permeability were (m^2): $2{\cdot}2 \times 10^{-13}$, $8{\cdot}5 \times 10^{-14}$ and $1{\cdot}0 \times 10^{14}$ respectively; for 25% massing water concentration the respective values were: $1{\cdot}0 \times 10^{-12}$, $1{\cdot}0 \times 10^{-13}$ and $1{\cdot}0 \times 10^{-14}$. The cumulative % oversize distribution of pores in lactose tablets of 26·5% porosity made from $-8+16$ mesh granules prepared by forced screening and comminution was 1·8, 1·7, 63·0, 63·0; 98·4, 98·6 respectively for each kind of granule for pore diameters of 20·00, 0·20, 0·02 μm.

Thus although the method of subdivision of a wet mass, to produce granules would appear to affect the packing characteristics of the granules, it does not effect tablet pore structure.

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The influence of synthetic "Substance P" on tremor caused by LSD in mice

Stern and Hadzović (1973) have recently shown that synthetic "Substance P" (SSP) (Tregear, Niall & Potts, 1971) passes through the blood-brain barrier, reduces aggressivity in mice and antagonizes abstinence symptoms in morphinized mice. Earlier it had been shown that impure "Substance P" (SP) potentiated the effect of lysergic acid diethylamide (LSD) upon the isolated ileum of a guinea-pig (Krivoy, 1957) and that it also acted centrally by enhancing electric potentials of dorsal roots of the spinal cord in the cat (Krivoy & Kroeger, 1963). I have examined the effect of SSP on static tremor caused by LSD (Ahmed & Taylor, 1959) and excitement caused by amphetamine. Tremor was induced not only by LSD, but also by oxotremorine and harmine, both causing the static type of tremor, and also by guanethidine, which causes intentional tremor (Stern, Milenković & Cetinić, 1970).

Mice of either sex, (Pasteur institute, Novi Sad) 20 ± 2 g were used. SSP was dissolved in 0·1 N acetic acid and administered at a dose of 0·5 mg kg^{-1} (i.m.) Controls were given the solvent. I also examined the effect of SSP on the concentration of acetylcholine in mouse brain (MacIntosh & Perry, 1950). This was considered necessary because the quantity of acetylcholine in the cns is of great importance for understanding the origins of tremor.

All the substances examined were administered 15 min after SSP, SSP doses smaller than 500 μg kg^{-1} i.m. could not cure either static or intentional tremor in mice. SSP does not cause tremor alone, even in doses between 100 and 2000 μg (i.m.)

The intensity of both static and intentional tremors was observed independently by 2 persons, neither of whom knew which group of animals was experimental and which was control.

Table 1 shows that SSP potentiates oxotremorine and LSD tremor. Tremor caused by oxotremorine can be abolished by atropine whilst tremor caused by LSD is unmodified.

As shown previously for SP (Zetler, 1956), SSP abolishes harmine induced tremor. The same effect was observed in animals that were excited by amphetamine. SSP has no effect on the intentional tremor caused by guanethidine.

SSP raises acetylcholine in mouse brain significantly 60 min after SSP has been administered (control value (μg g^{-1} fresh tissue): $2{\cdot}35 \pm 0{\cdot}2$ n = 5; animals injected

Table 1. *The influence of SSP upon tremor and unrest in mice (measured 15 and 30 and 60 min after SSP was administered).*

Substance	Dose (mg kg^{-1}, i.p.)	SSP (mg kg^{-1}, i.m.)	No. of animals	The effect on tremor
LSD	3		12	++
LSD*	6		12	++++
LSD*	3	0·5	16	++++
LSD*	3			
Atropine HCl	10	0·5	12	++
LSD*	3	1·0	12	++++
LSD*	6	0·5	6	++++
Oxotremorine	0·25 (i.v.)		10	++
Oxotremorine	0·25 (i.v.)	0·5	10	++++
Harmine HCl	30		10	++
Harmine HCl	30	0·5	10	−
Guanethidine sulphate ..	25		10	++
Guanethidine sulphate ..	25	0·5	10	0
Amphetamine HCl ..	5		8	++
Amphetamine HCl ..	5	0·5	8	−

* Tremor was strongest after 15 min. ++ Intensity of tremor in controls. ++++ Tremor potentiated. 0 No effect on tremor. − Tremor abolished.

i.m. with 0·5 mg kg^{-1} SSP: 2·95 $\pm$ 0·1 n = 6; $P < 0{\cdot}05$). It should be mentioned that Radmanović & Rakić (1965) found that paraoxon, a cholinesterase inhibitor which penetrates the blood-brain barrier, decreases brain level of SP in rabbits. The potentiation of oxotremorine or LSD-induced tremor after SSP has been administered, could be explained by the increase in brain acetylcholine. It should be stressed, however, that LSD does not increase the concentration of acetylcholine in the cns (Giarman & Pepeu, 1962) whilst oxotremorine does (Holmstedt, Lundgren & Sundwall, 1963).

It is noteworthy that the concentration of SP is highest in the corpus striatum (Lembeck & Zetler, 1967), in the region that is held responsible for originating tremor. Harmine tremor is not abolished by atropine (Cox & Potkonjak, 1971). Since SSP potentiates LSD tremor but abolishes excitement caused by amphetamine. The question is, therefore, does SSP also potentiate any other psychic effects of LSD? If it does, SSP could be used eventually in the manner of nalorphine but for the detection of LSD in man.

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Modification by caerulein of action potential activity in circular smooth muscle of isolated small intestine

Caerulein appears to be one of the more active gall-bladder contracting agents known at present and exhibits a potent stimulant action on the musculature of the gut (Erspamer, 1970, 1971). Moreover cholecystokinin-pancreozymin (CCK) whose C-terminal octapeptide shows a close resemblance to caerulein, affects intestinal motility in a way very similar to that of caerulein (Hedner, 1970). In the isolated intestine the efficiency of the peristaltic reflex is increased by caerulein (Frigo, Torsoli & others 1972) and propulsion of the intraluminal content is favoured at concentrations of caerulein much lower than those necessary to elicit contraction of the longitudinal muscle (Frigo, Lecchini & others, 1971). However no investigation has been made on the effect of caerulein on the electrical activity of the isolated small intestine.

The electrical activity of the small intestine as recorded with extracellular electrodes consists of rhythmic fluctuations of resting membrane (slow waves) and of rapid action potentials (spikes) which appear during slow wave depolarization (Baker, 1969; Bortoff, 1972). Spikes are accompanied by contraction of muscular layers and it has been found that the spikes synchronous with the contraction of circular fibres always occur after spike activity of the longitudinal fibres (Gonella, 1971). We now describe some experiments on the action of caerulein on the electrical activity made with a view to elucidating the mechanism by which caerulein improves propulsive activity.

Rabbits of either sex, 900–1200 g, were used. A piece of ileum, 5–6 cm length, was mounted in a horizontal bath containing Tyrode solution aerated with 5% carbon dioxide in oxygen, at 36°. Longitudinal contractions, intraluminal pressure and extracellular electrical activity were recorded as described by Gonella (1971). The frequency of the slow waves was 8–16 min^{-1} and the amplitude ranged from 2 to 4 mV. Each slow wave shows a burst of spikes of 4–6 mV associated with longitudinal contractions (Fig. 1). similar to those obtained from isolated longitudinal muscle by Gonella, (1970) and by Small & Weston (1971). Faster action potentials of 6–10 mV occurred occasionally after that of longitudinal muscle and were associated with localized contraction of circular muscle. As shown in Fig. 1, caerulein added to the bath at a final concentration of 0·2 ng ml^{-1} affected neither the frequency and the amplitude of slow waves nor the size of the spikes associated with longitudinal contractions. On the contrary in all preparations (30 expts) using concentrations of caerulein from (0·1–0·5 ng ml^{-1}) the frequency and the amplitude of action potentials associated with circular contractions were increased. The addition of caerulein to the bath caused the appearance of trains of spikes after a latency of 15–30 s and the action disappeared after 5–10 min. Development of tachyphylaxis could not be observed in any of the preparations. CCK added to the bath at final concentrations ranging between