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THE EFFECT OF LYSERGIC ACID DIETHYLAMIDE ON SOME AUTONOMIC REFLEX PATTERNS

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The effects of *d*-lysergic acid diethylamide (LSD) on mental function in man are often accompanied by fluctuating autonomic reactions. An experimental approach was attempted in order to obtain some information on this aspect of the action of LSD. Three different types of autonomic reflexes: vascular, respiratory and intestinal were chosen and the effects of LSD on these investigated.

At the same time it was hoped to establish a relatively simple and reproducible response pattern specific for LSD and those derivatives of LSD capable of producing a psychological change. Such a response could be expected to constitute a suitable pharmacological test for detecting LSD-antagonists.

This hope, however, has not been fulfilled. All actions produced by LSD were also observed after administration of lysergic acid derivatives lacking psychological effects. As a representative of the latter, BOL-148, the 2-brom-derivative of LSD was regularly included in any investigation. The advantage of this substance was a close chemical relationship to the parent compound on the one hand, and, on the other, an anti-5-hydroxytryptamine (5-HT) action of the same order of magnitude as seen with LSD, (CERLETTI AND KONZETT[1]).

The following derivatives of *d*-lysergic acid were used in this study: the diethylamide (LSD-25) as the tartrate, its 2-brom-derivative (BOL-148) as the bitartrate, the monoethylamide (LAE-32) and the pyrrolidide (LPD-824), both as the bimaleate, the 1-methyl- and 1-acetyl-derivative of LSD-25 (MLD-41 and ALD-52), both as the bitartrate.

VASOMOTOR REFLEXES

In a series of experiments, started in 1955 (GINZEL[10,11]), cats were used in chloralose or barbiturate anaesthesia and injections were made either into the lateral ventricle of the brain through a Feldberg-Sherwood cannula (FELDBURG AND SHERWOOD[7]) or intravenously. The vagi were sectioned in most experiments. Artificial respiration was employed throughout to maintain constant respiratory conditions irrespective of a possible reduction of spontaneous respiration as seen with LSD in preliminary experiments.

Pressor responses were elicited by one of the following procedures: electrical stimulation of an afferent nerve, asphyxia, occlusion of both common carotid arteries, injection of nicotine to the carotid chemoreceptors and electrical stimulation of one carotid sinus nerve.

These pressor responses could be reduced or abolished by intraventricular or intravenous injection of LSD in doses of 100–200 μg and 60–100 μg kg respectively. The volume of the injections was kept within 0.1–0.2 ml; control injections were

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without effect. The time of onset was 1–3 minutes; the effects lasted between 30 and 60 minutes, when complete recovery was usually obtained.

The blocking action of LSD on these reflexes was accompanied by an effect of the drug on the arterial pressure which varied between moderate rise and pronounced fall. The latter was not prevented by vagotomy and atropinisation, and appeared therefore (a direct vasodilator effect of LSD being excluded) to depend on a diminution of central vasomotor tone.

The fact that LSD induced changes in systemic pressure made it difficult to assess the mechanism by which it reduced the carotid pressor reflex whose actual size is partly related to the pressure level at the time. Any influence, chemical or physical, which lowers the blood pressure within a certain range will of necessity reduce the response to carotid occlusion.

This response is a composite phenomenon consisting of the decrease of the pressure-dependent baroreceptor inhibitor tone and the initiation of chemoreceptor discharges due to the hypoxia condition, developing within the carotid body during clamping (VON EULER AND LILJESTRAND[2]; LANDGREN AND NEIL[18]). Both events increase the activity of the medullary vasomotor centre resulting in the pressure rise.

To elucidate this point further, the two components of the reflex were separated by allowing the animal to breathe air and pure oxygen alternately. Under oxygen no hypoxia can develop; therefore, only the baroreceptor response is left. The difference in the height of the pressor reflex during air and oxygen breathing, revealing the part played by the chemoreceptors at the time, was abolished by LSD indicating an interruption of the chemoreceptor pathway. The remaining baroreceptor reflex, however, was frequently reduced or abolished as well, but this permitted no conclusion as to whether the baroreceptor pathway itself was also blocked or whether the reduction occurred simply as a consequence of a fall in systemic pressure. The abolition of the chemoreceptor component of the occlusion reflex was always accompanied by the disappearance of the pressure rise elicited by close arterial injection of nicotine or potassium cyanide to the carotid chemoreceptors.

Such an experiment is shown in Fig. 1. The carotid occlusion response was in that case predominantly due to the stimulation of the chemoreceptors by oxygen lack since it dwindled to a small rest during oxygen breathing. After an injection of 200 μg of LSD into the lateral ventricle of the brain the large chemoreceptor component of the reflex and, at the same time, the response to nicotine were blocked.

A depressor response to electrical stimulation of one carotid sinus nerve involves neurones arising from baroreceptors only. This response was not suppressed by LSD in a dose which abolished the pressor response to carotid occlusion. In experiments where electrical stimulation of one sinus nerve was followed by a blood pressure rise, LSD caused a conversion of this pressor into a depressor response. The chemoreceptor impulses which predominated before LSD was given, were blocked, and thus impulses elicited in baroreceptors fibres during stimulation determined the effect now observed (GINZEL[12]).

Injection of LSD into the carotid sinus did not diminish the excitability of the receptors situated there, neither did LSD affect the peripheral part of the efferent pathway of the reflex. LSD was still effective in blocking the chemoreceptor reflex when the brain stem was severed at intercollicular level. The effect, however, appeared then to be dependent on the presence of chloralose.

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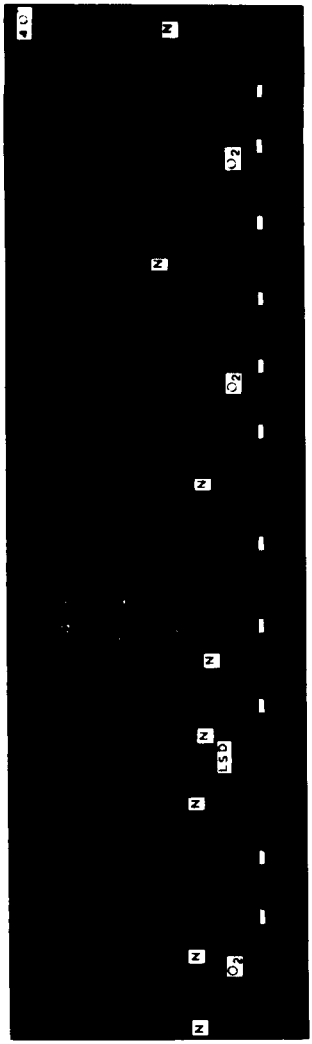

Fig. 1

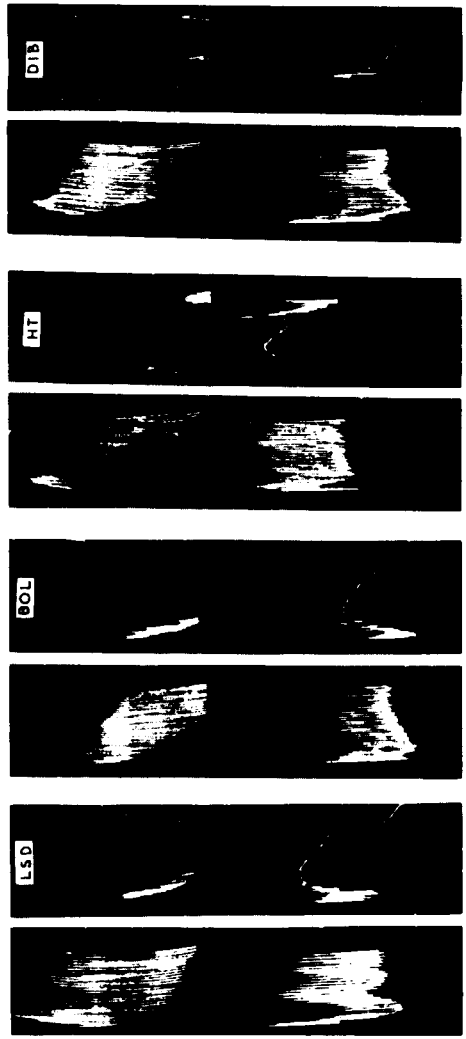

Fig. 2

Fig. 1. Cat 2.1 kg, chloralose anaesthesia. Both vagi cut. Artificial respiration. Injections each of 5 μg of nicotine at N into right carotid sinus region through a cannula tied into inguinal artery. Records from above are: Blood pressure (femoral artery) in mm Hg, marks indicating periods of oxygen breathing, injection marks; and white bars indicating the clamping of both common carotid arteries for 45 sec; time in 30 sec. White dot marks injection of 200 μg LSD into lateral ventricle of brain. The responses, blocked by LSD, are fully restored about half an hour after the injection.

Fig. 2. Guinea-pig ileum preparation suspended in 50 ml Tyrode solution. The upper tracing represent the changes in intestinal volume, recorded by means of a piston recorder, each downward dejection signifies filling of the lumen, each upward dejection expulsion of the fluid. The lower record shows the contractions of the longitudinal muscle. The peristaltic reflex was elicited by raising the intraluminal pressure to 2.5 cm. Each of the four sections of the tracing contains a control reflex, and the reflex in the presence of a blocking compound. LSD in a concentration of 10^{-6}, BOL-148 5.10^{-7}, 5-HT 8.10^{-7}, Dibenamine (DIB) 10^{-6}.

The above evidence suggested a specific central interruption by LSD of the carotid chemoreceptors — medullary vasomotor centre(s) — sympathetic vasoconstrictor fibres-reflex.

BOL-148 exhibited a similar blocking action when injected into the lateral ventricle, but was about half as potent as LSD. Lysergic acid pyrrolidide, PLD-824, which is also devoid of mental effects, was equipotent with LSD. Of the two psychologically active derivatives tested, the lysergic acid monoethylamide, LAE-32, possessing only a tenth of the psychotropic potency of LSD, surpassed the reflex blocking effects of the latter by 2–5 times whereas the 1-acetyl-lysergic acid diethylamide, ALD-52, failed to exert any of the described blocking actions. Thus correlation was lacking not only between the mental and the reflex blocking effects of these substances but also as regards their anti-5-HT properties (Table 1).

TABLE I

	Psychotropic action	*Anti-5-HT action (rat uterus)*	*Blocking effect on vasomotor reflexes*	*Blocking effect on peristaltic reflex*
LSD-25	+	1*	1	1
BOL-148	0	1–5*	$\frac{1}{2}$	2
LAE-32	+ $(\frac{1}{10})$	$\frac{1}{8}$*	2–5	1
LPD-824	0	$\frac{1}{20}$*	1	
ALD-52	+	2*	0 (500 μg)	$\frac{1}{10}$
MLD-41		3·7*		$\frac{1}{10}$ – $\frac{1}{5}$
Ergotamine	0			$\frac{1}{5}$
Dihydroergotamine	0	$\frac{1}{4}$§	0 (200 μg)	$\frac{1}{5}$
Dibenamine	+	1·2§		1
Chlorpromazine	+	1	1	$10–10^6$
5-HT	+		0 (1 mg)	$\frac{1}{10}$ – 10

The figures express the relative potency of the substances, referring to that of LSD as 1.

* Personal communication.

* CERLETTI AND KONZETT[1].

§ GADDUM *et al.*[9].

VON EULER AND SCHMITERLÖW[3] have shown that ergotamine inhibited selectively the carotid baroreceptor reflex. Confirming this, it was observed that the remaining part of the carotid occlusion response after a dose of LSD which blocked the chemo-

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receptor reflex, disappeared promptly when ergotamine was injected. Also the baroreceptor depressor reflex could then no longer be elicited. Thus two alkaloids of the same family, both containing lysergic acid as basic building stone in their chemical structure, appear to have a specific blocking effect on either a chemo- or a baroreceptor reflex pathway.

5-HT was administered to the ventricle in doses up to 1 mg but neither influenced the reflex responses as such nor prevented or counteracted their inhibition by LSD. 5-HT has, however, been reported to stimulate carotid chemoreceptors (GINZEL AND KOTTEGODA[15]; MCCUBBIN, GREEN, SALMOIRAGHI AND PAGE[19]). This peripheral stimulant action was abolished by local injection of LSD which left the chemoreceptors otherwise sensitive towards nicotine and the psychological stimulus of oxygen lack (GINZEL[13]).

Chlorpromazine, which had been shown before to interfere with vasomotor responses (DASGUPTA AND WERNER[4]), was found equally effective as LSD in blocking the vasomotor component of the carotid chemoreceptor reflex when the intraventricular route was used. No such action, however, could be observed after intravenous injections of doses (up to 2 mg/kg) which did not yet affect the efferent limb of the reflex.

RESPIRATORY REFLEXES

Respiratory responses arising from the carotid chemoreceptors were not selectively blocked by LSD. An overall depression of respiration occurred after LSD which still permitted distinct although correspondingly lowered responses to intracarotid injection of nicotine or potassium cyanide and the breathing of 5 % carbon dioxide.

It is interesting to note that LSD thus distinguished between pathways originating in the same peripheral receptor organ, leading to two different central autonomic relay stations, the respiratory and the vasomotor centre.

PERISTALTIC REFLEX

Two considerations determined the choice of this particular preparation. Since the demonstration of the blocking action of morphine and all strong analgesics on the peristaltic reflex of the guinea-pig ileum (SCHAUMANN, GIOVANNI AND JOCHUM[21]) experimental evidence has been accumulating that the nervous system of the gut reacts in some respects similarly to the central nervous system, and may thus serve — with due limitation — as a less complicated model of the latter. It seemed therefore worth investigating whether a compound so highly active on the brain as LSD would influence the neuronal network underlying the peristaltic reflex.

The second suggestion came from a different direction of thought. We are still puzzled by the high amounts of 5-HT in the intestine and do not know whether this substance plays a role in the physiological function of the gut or not. If 5-HT is essential for the intestinal function, an effect of it on the peristaltic reflex might be expected; the same should then apply also to antagonists to 5-HT, and there we cross the path of LSD again.

Pieces of the guinea-pig's lower ileum were removed from the freshly killed animal and mounted in a 50 ml tyrode bath at 37° according to the method of

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TRENDELENBURG[22]. The bath was aerated with a mixture of 95 % oxygen and 5 % carbon dioxide. The peristaltic reflex was elicited by raising the intraluminal pressure from 0 to 2 or 3 cm H_2O.

The first response to intraluminal pressure rise is a shortening of the longitudinal muscle fibres termed by TRENDELENBURG as the preparatory phase. When a threshold value of about 1.5 cm is reached rhythmic contractions of the circular muscle layer ensue, spreading as peristaltic waves from the oral to the aboral end of the gut. This second phase was called the emptying phase.

It was found (GINZEL[14]) that LSD abolished this emptying phase of the reflex, while the preparatory phase remained unimpaired (Fig. 2). The effective concentrations ranged between 10^{-6} and 5.10^{-6}. BOL-148 blocked the peristaltic waves in even lower concentrations (5.10^{-7} to 2.10^{-6}). LAE-32 had about the same potency as LSD, while the methyl- and acetyl-derivative of LSD (MLD-41 and ALD-52 respectively) were less consistent and generally weaker active on the reflex. Ergotamine and di-hydro-ergotamine inhibited the emptying phase in concentrations of about 10^{-5} (Table I).

In order to find out whether the blocking effect of these compounds was related to their chemical configuration or to their anti-5-HT action, other potent 5-HT antagonists of different structure were tested. Dibenamine, which is a potent antagonist of 5-HT (GADDUM, HAMEED, HATHWAY AND STEPHENS[9]), blocked the emptying phase of the reflex in similar concentrations as LSD (Fig. 2). Chlorpromazine, which possesses also considerable 5-HT antagonistic effects (GYERMEK, 1955; BENDITT AND ROWLEY, 1956), exerted a powerful blocking action: concentrations as low as 10^{-8} were sometimes sufficient to inhibit the reflex; sometimes, however, concentrations of 10^{-8} to 10^{-6} were required. No explanation could yet be found for this great variability in sensitivity. Chlorpromazine also impaired the preparatory phase, sometimes even at an earlier stage than the emptying phase.

Usually the paralysing action of these compounds on the peristaltic reflex decreased during the course of an experiment, which made it difficult to determine dose-response curves for these substances. A further difficulty in comparing these blocking compounds quantitively resulted from cross-tolerance which seemed to develop. The figures in the table must therefore be regarded as approximate values.

Cocaine and tubocurarine (FELDBERG AND LIN[6]) and hexamethonium (PATON AND ZAIMIS[20]) block the emptying phase of the peristaltic reflex and abolish at the same time the response of the longitudinal muscle to nicotine and barium chloride; the effects of the latter substances on the guinea-pig ileum are mainly of ganglionic origin (FELDBERG[5]). All the blocking substances investigated here inhibited also the contractions produced by nicotine and barium chloride in concentrations which paralysed the peristaltic waves. They did not reduce or only slightly reduced the contraction elicited by acetylcholine; chlorpromazine, however, frequently antagonised the action of acetylcholine as well.

LSD and BOL-148 were then applied by close arterial injection to the superior cervical ganglion of the cat. No block of transmission in this ganglion was observed and neither substance diminished the depressor effect of peripheral vagus stimulation. Chlorpromazine has likewise been shown to lack a peripheral ganglionic blocking action (HOLZBAUER AND VOGT[16]). These findings suggest that the similarity between hexamethonium and LSD as to their effects on the guinea-pig ileum is not based on a similar mechanism of action.

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All 5-HT antagonists so far tested were found to block the peristaltic reflex. This finding thus raised the question whether they do so by interfering with a mechanism dependent on 5-HT.

An effect which is produced or mediated by 5-HT is also counteracted by 5-HT, when applied in larger doses. For example, the contraction of the guinea-pig ileum elicited by 5-HT in a small dose disappears after large doses of 5-HT or tryptamine (GADDUM[6]). Responses of the smooth muscle to other stimulant substances, however, remain unaffected; this led to the postulation of special "tryptamine receptors" and to the idea that saturation of these receptors by 5-HT or tryptamine abolishes the action of either substance. If the above consideration is valid, excess of 5-HT should then interfere with the reflex in a similar way as 5-HT antagonists did.

Indeed, it was found that 5-HT blocked the emptying phase of the reflex (Fig. 2). The concentrations varied over a wide range (from 10^{-7} to 10^{-5}) in different preparations and tolerance developed easily with repeated exposures of the organ to the drug. The initial shortening of the muscle remained unchanged as with all 5-HT antagonists apart from chlorpromazine. In contrast to LSD, however, the nicotine contractions were not suppressed when the peristaltic reflex was paralysed in the presence of 5-HT.

The blockade of the reflex by 5-HT developed regardless of whether the blocking dose of 5-HT caused a contraction on addition to the bath, or failed to do so owing to the desensitization of the preparation by the preceding doses of 5-HT.

The findings that 5-HT did not interfere with the preparatory phase agrees with an earlier observation by KOSTERLITZ AND ROBINSON[17], who studied the mechanism of the longitudinal contraction elicited by raising the pressure in the lumen. During the preparation of this manuscript an article by these authors appeared (KOSTERLITZ AND ROBINSON[17]) which contains results on a blocking effect of 5-HT on the emptying phase of the peristaltic reflex.

LSD blocks the reflex in a dose which does not abolish the contraction due to added 5-HT. 5-HT, in a certain dose range, can block its own effect without yet inhibiting the reflex. BOL-148 suppresses both at the same time. If thus the 5-HT antagonists should exert the reflex blocking effect through their anti-5-HT action, two different receptors of 5-HT in the gut must be assumed; one of them may play a part in the peristaltic reflex and be blocked by large doses of 5-HT.

CONCLUSIONS

LSD has been shown to block vasomotor reflexes by a central action, probably below the intercollicular level, and to inhibit the emptying phase of the peristaltic reflex in the isolated guinea-pig ileum.

Both actions, however, are unlikely to have any bearing on the effects of LSD in man, including those on automatic functions, or to involve a mechanism similar to that underlying the mental effects of the compound. The reasons for this are as follows:

The concentrations of LSD required to cause impairment of these reflexes are considerably higher than those that can be expected to occur at the respective sites in man after ingestion of so little as 50–100 μg of the substance. In contrast, the concentration of morphine that blocks the peristaltic reflex agrees well with the value calculated for human tissues after administration of the drug.

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Furthermore, the observed blocking actions were not limited to LSD but could also be obtained with derivatives of LSD which do not produce mental changes.

However disappointing these conclusions may be, the lack of positive information towards the initial aim of this investigations was well compensated for by the following two findings:

1. The action of LSD on the carotid occlusion reflex constitutes a specific action on the chemoreceptor component of the reflex; ergotamine, however, though deriving from the same chemical structure, predominantly affects the bararoreceptor component of the reflex.

Thus it appears possible to differentiate by pharmacological means between pathways connecting either two different types of peripheral receptors to one central neuronal pool — as it were: the baro- and chemoreceptors to the vasomotor centre — or, with regard to the lacking effect of LSD on the respiratory chemoreceptor reflex, *one* set of peripheral receptors — the carotid chemoreceptors — with *two* different *central* sites, the respiratory and the vasomotor centres of the medulla.

2. LSD blocked the peristaltic reflex and so did other 5-HT antagonists with or without chemical relationship to LSD. The blocking effect resembled that of hexamethonium but no ganglionic blocking action was revealed when tested on the superior cervical ganglion.

5-HT, which can counteract its own actions by desensitizing the respective receptors, also blocked the emptying phase of the reflex.

Thus a new group of substances can be postulated which act on those neuronal circuits of the guinea-pig ileum that underlie the rhythmic contractions of the circular-muscle resulting in peristaltic waves.

The evidence would tempt one to speculate on the possibility of 5-HT playing a part in the peristaltic reflex.

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SUMMARY

The effect of LSD-25 has been tested on 3 different kinds of autonomic reflexes: vasomotor, respiratory and intestinal.

Vasopressor responses such as following stimulation of an afferent nerve, asphyxia, carotid occlusion or carotid chemoreceptor excitation were suppressed by 100–200 μg LSD-25 injected into the lateral ventricle of the cat's brain. An analysis of the action on reflexes mediated through the carotid sinus nerve led to the conclusion that the chemoreceptor pathway appears to be selectively blocked by LSD-25 centrally below the intercollicular level. This is also true after intravenous administration of the drug.

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No specific interruption of a chemoreceptor pathway could be detected with respiratory responses arising from the chemoreceptors. An overall depression of respiration occurred after LSD-25, which still permitted distinct, although correspondingly lowered responses to intracarotid injection of nicotine or potassium cyanide and breathing of 5 % CO_2.

The peristaltic reflex constitutes an autonomic neuronal circuit which may in several respects serve as a comparatively simple model of neuronal networks of the brain. Employing the technique of TRENDELENBURG, the peristaltic reflex was elicited in the guinea-pig ileum by raising the intraluminal pressure. LSD-25 was found to inhibit the emptying phase of the reflex, and suppress the response of the intestinal muscle to nicotine at the same time. Though this action resembled closely that of ganglionic blocking drugs, LSD-25 had no ganglionic blocking effect when tested on the superior cervical ganglion.

The reflex blocking effects of LSD-25 as described above were also produced by other derivatives of lysergic acid, independent of whether they have any psychological action or not. Moreover, chlorpromazine was found to have the same reflex blocking effects as LSD-25.

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