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# THE EFFECT OF (+)-LYSERGIC ACID DIETHYLAMIDE AND OTHER DRUGS ON THE CAROTID SINUS REFLEX

BY

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In cats, lysergic acid diethylamide (LSD) selectively blocked the reflex blood pressure rise following carotid chemoreceptor stimulation. It also reduced or abolished the chemoreceptor component of the pressor response to occlusion of the common carotid arteries. It did not inhibit the respiratory reflexes arising from the carotid chemoreceptors, unless spontaneous respiration was interfered with as a whole. The site of action was central, probably below the intercollicular level, regardless of whether the drug was administered by the intravenous route or into the lateral ventricle of the brain.

LSD did not block the baroreceptor depressor reflex elicited by stimulation of one carotid sinus nerve. LSD frequently caused the systemic pressure to fall, even after vagotomy and atropine, and this effect might account for the occasional reduction of the baroreceptor component of the carotid occlusion response. On the other hand, no relationship was found between the action of LSD on vasomotor tone and its blocking effect on the chemoreceptor pressor reflex.

Some derivatives of LSD produced effects similar to those described for LSD, whether or not they possessed a psychotropic action in man, and independently of their efficiency as antagonists to 5-hydroxytryptamine. Of a series of compounds chemically unrelated to LSD, chlorpromazine was found to block the chemoreceptor pressor rise after intracerebroventricular injection.

In two preliminary communications it has been reported that (+)-lysergic acid diethylamide (LSD) is capable of blocking vasomotor reflexes (Ginzel, 1955, 1956). The investigation was particularly concerned with those reflexes which arise from receptors of the carotid sinus region. A detailed account of this work is presented here, including the action of some derivatives of LSD and other substances without chemical relationship to LSD.

## METHODS

Fifty cats were used, anaesthetized by intraperitoneal administration of chloralose (70 to 80 mg./kg. body weight). Five experiments were performed using pentobarbitone sodium anaesthesia, and four cats were decerebrated when anaesthetized with chloralose or ether. The blood pressure was measured by means of a mercury manometer connected into one femoral artery. Heparin was injected intravenously in all animals. The trachea was cannulated and, apart from a few experiments where spontaneous respiration was recorded, the animals were respired artificially through an "Ideal" respiration pump. Provision was made to supply the inlet of the pump with either air or pure oxygen.

Both common carotid arteries were dissected free from the surrounding tissues for a length of about 2.5 cm. below the level of the thyroid artery which was cut between ligatures; rubber-covered clamps could therefore easily be applied to the vessels without causing undue stretching. One lingual artery was prepared and a tap cannula was inserted, the tip pointing towards the carotid sinus; through this cannula arterial injections could be made in close proximity to the baro- and chemo-receptors of this region. In order to stimulate the chemoreceptors, small amounts (each dissolved in 0.1 ml. saline) of potassium cyanide, nicotine, or the bis-choline-ester of sebacinic acid (Österreichische Stickstoffwerke A.G., Linz) were injected. The last-named substance is a powerful nicotine-like stimulant drug and is hydrolysed by pseudocholinesterase at a rate similar to that of acetylcholine (Ginzel, Klupp, and Werner, 1952); it is probably because of this high rate of breakdown that it does not show any secondary paralysing effects like nicotine when injected repeatedly in quick succession. It proved, therefore, particularly advantageous when constant responses

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were desired throughout the course of an experiment lasting several hours. During the injections, the external carotid artery was temporarily occluded.

In some experiments, one carotid sinus nerve was dissected and placed on a shielded electrode for electrical stimulation by means of the secondary coil of an inductorium.

Pressor responses were elicited by one of the following procedures: asphyxia produced by clamping the tracheal tube for 60 sec., electrical stimulation of the central end of the cut sciatic nerve, stimulation of one carotid sinus nerve (Neil, Redwood, and Schweitzer, 1949), intra-arterial injection of stimulant drugs to the carotid chemoreceptors and, finally, occlusion of both common carotid arteries for 30 sec. The vagi were sectioned in most experiments in order to avoid activation of homeostatic reflexes from aortic receptors which would tend to counteract these pressor responses.

The substances investigated for their ability to modify the pressor reflexes were administered either intravenously or into the lateral ventricle of the brain through a cannula described by Feldberg and Sherwood (1953). The volume of the injections was kept within 0.1 to 0.2 ml., and regular control injections with saline, adjusted to the *p*H of the test solutions, were given. The position of the intracerebroventricular cannula was checked at the end of each experiment.

In several experiments, intravenous injections of nicotine, adrenaline, and noradrenaline were made before and after LSD, which was administered by either route. The pressor responses to these three drugs were used to test the function of the peripheral pathway at the levels of sympathetic ganglia and effector cells. In two experiments the preganglionic fibres of the superior cervical ganglion were stimulated electrically and the response of the nictitating membrane was recorded.

The following derivatives of (+)-lysergic acid were used in this study: the diethylamide (LSD 25) as the tartrate, its 2-bromo derivative (BOL-148) as the bitartrate, the monoethylamide (LAE 32) and the pyrrolidide (LPD 824) both as the bimaleate, and the (−)-acetyl derivative of LSD 25 (ALD 52) as the bitartrate. The substances, supplied in powder form by Sandoz, were dissolved in distilled water (1:500 or 1:1,000); the solutions were kept in a well-stoppered dark bottle at 0° and they retained their activity for at least a fortnight. 5-Hydroxytryptamine (May and Baker) was used as the creatinine sulphate and chlorpromazine (May and Baker) as the hydrochloride.

## RESULTS

*The Effect of LSD on Various Vasomotor Responses.*—LSD was found to reduce or block rises of the blood pressure which were elicited by the various procedures as described above. The doses ranged between 50 and 200 μg. for the intracerebroventricular injection, and between 50 and 100 μg./kg. body weight when given intravenously. In experiments performed during spring and early summer, the blocking doses of LSD injected intracerebroventricularly were usually around 200 μg. while the doses required in experiments later in the year lay between 50 and 100 μg.

The time of onset of the blocking action of LSD was short, ranging between 1 and 3 min. in different experiments; the maximum effect was reached within 5 to 20 min. Complete recovery was obtained in most experiments between ½ and 1 hr. and the injection of LSD could then be repeated once or twice with comparable results.

The reduction by 200 μg. of LSD in the responses to occlusion of both common carotid arteries and to electrical stimulation of the central stump of the cut sciatic nerve can be seen in Fig. 1. When the reflexes had regained their

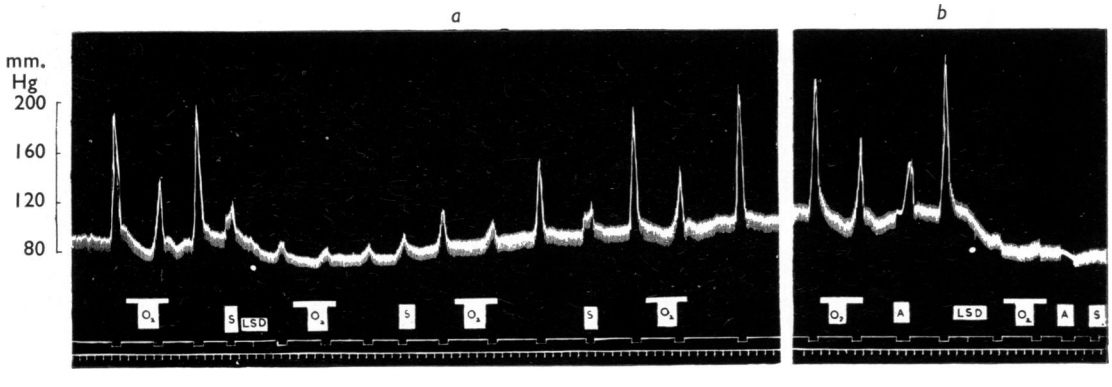


FIG. 1.—Cat, 3.2 kg., chloralose anaesthesia. Both vagi cut, artificial respiration. Records from above down: blood pressure in mm. Hg. The signal alone indicates periods of carotid occlusion; or at S, sciatic nerve stimulation, or at A, asphyxia alone. The horizontal white bars indicate ventilation with oxygen for 2½ min. Time, 30 sec. Between *a* and *b* 10 min. interval. At white dots, injections into the lateral ventricle of the brain of 200 μg. of LSD.

initial size about ½ hr. after the first injection, a second intracerebroventricular injection of the same dose (Fig. 1, *b*) was given and caused a complete block of the pressor responses. This indicated a slight cumulative effect which was, however, not a regular feature. Sometimes a decrease rather than an increase of the blocking action of LSD was observed on repeated administration of the drug. Fig 1, *b* also shows the blocking effect of LSD on the rise of systemic pressure produced by asphyxia.

The effect of LSD on the pressor response to stimulation of the carotid chemoreceptors by intra-arterial injection of sebacinyl-bis-choline (N) is shown in Fig. 2. 150 μg. of LSD, injected into the lateral ventricle, abolished these pressor responses whereas the same dose of LSD previously given intravenously was without effect on the reflex. The chemoreceptor pressor reflex elicited by potassium cyanide was also blocked by LSD.

In the experiment shown in Fig. 2, LSD caused the pressure to fall by about 50 mm. Hg; more or less (Fig. 1) pronounced depressor effects were seen in other experiments, but occasionally no noticeable change in pressure occurred. The strength of the vasodepressor effects of LSD did not appear to be related to the strength of its blocking action on these reflex responses: thus a small reduction of a reflex could be associated with a great blood pressure fall and the reverse was also true. Moreover, the respective strength of these effects changed sometimes during the course of an experiment. The LSD-induced blood pressure fall was not diminished by vagotomy and atropine.

The actual size of the carotid occlusion reflex depends, at least in part, on the blood pressure level at the time; any influence, chemical or physical, which lowers the pressure will therefore, of necessity, reduce the response to carotid occlusion.

*The Effect of LSD on the Carotid Occlusion Reflex.*—Two factors are responsible for the rise in pressure following occlusion of one or both common carotid arteries. One is the reduction in baroreceptor impulses owing to the reduced pressure in the sinus region above the point of clamping; thus the vasomotor centre, normally inhibited by the baroreceptor impulse traffic, escapes this inhibition and increases its activity. This increase reveals what has been termed the "pressor reserve" and is the greater, the greater the systemic pressure (and consequently the baroreceptor inhibitor tone) was prior to the clamping procedure. The second factor is the increased chemoreceptor impulse activity resulting from the hypoxic condition which develops within the carotid body when the normal blood flow is reduced during clamping (von Euler and Liljestrand, 1943; Landgren and Neil, 1951a).

If, therefore, a drug modifies the carotid occlusion reflex (COR) further information as to the nature of this effect should be sought by investigating the two components of the COR separately. This can be achieved when the animal is allowed to breathe air and pure oxygen alternately. Under oxygen, no local hypoxia of the glomus cells develops during the 30 sec. of clamp-

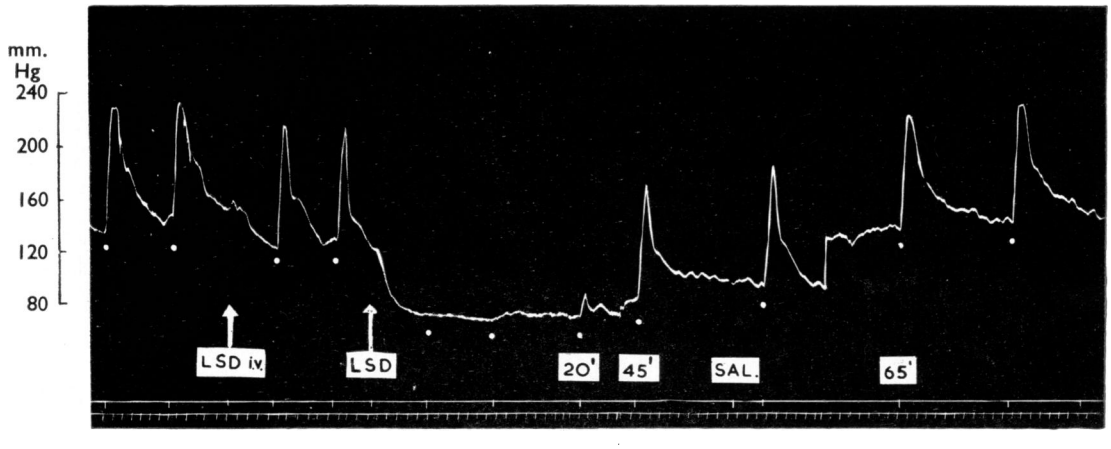


FIG. 2.—Cat, 2.9 kg., chloralose anaesthesia. Both vagi cut, artificial respiration. Traces from above down: blood pressure; injection signal; time, 30 sec. (irregularity in time tracing was due to a mechanical fault in the kymograph). Each white dot indicates injection into the lingual artery of 10 μg. of sebacinyl-bis-choline. Two doses of LSD, each of 150 μg., were given, the first by the intravenous and the second by the intracerebroventricular route. At SAL, 0.1 ml. of saline was injected into the lingual artery. The numerals give the time intervals in min. after the injection of LSD.

ing, the COR being almost entirely baroreceptor in function (Landgren and Neil, 1951b). The height of the COR under air breathing will be increased by the extent to which chemoreceptors contribute to the COR at the time. It will be found that, in the beginning of an experiment with a higher systemic pressure, none or only a small fraction of the COR is due to chemoreceptor activation; towards the end, however, with a gradually falling arterial pressure, the chemoreceptor part of the reflex is increased, whereas that due to changes in baroreceptor activity is diminished. Hence it is conceivable that even at different pressure levels two equally large responses may occur which, in fact, can be shown to be different in respect of the individual size of their contributory factors. It is clear that much caution and criticism are necessary if the effects of a drug on the COR are to be determined.

In Fig. 1, the COR was elicited under air and oxygen breathing respectively. The difference in the height of these reflexes indicated the part played by chemoreceptor activation. After the injection of LSD this difference disappeared; in this experiment, however, the COR had dwindled to such a small residual size that it was not easy to study this particular aspect here. Fig. 3 shows an experiment in which the effects of LSD on the two components of the COR and on the response to N were tested alternately. In this experiment the COR elicited during oxygen breathing was about half as great as that elicited during air breathing. Immediately after the injection of 200 $\mu$g. of LSD into the lateral ventricle, the systemic pressure dropped by about 25 mm. Hg and none of the reflex responses could be produced. A few minutes later, when the pressure had regained its initial level, the COR was restored to the height seen during oxygen breathing prior to the injection of LSD. Oxygen breathing reduced the COR now only by about $\frac{1}{6}$, indicating that the chemoreceptor component of the COR was almost abolished. At the same time the chemoreceptor reflex elicited by close arterial injection of N was absent, only reappearing with reappearance of the difference in the height of the COR.

Thus, it is apparent that there exists a stage in the action of LSD where the COR is reduced owing to the abolition of the chemoreceptor contribution. The remaining baroreceptor reflex, however, was also frequently reduced or abolished in the early phase of the effect of LSD, as seen for example in Fig. 3. The reduction might have been simply the consequence of the LSD-induced fall in systemic pressure, which, *per se*, lowers the baroreceptor inhibitor tone and thus diminishes the pressor response during clamping. In the experiment shown in Fig. 1, however, the depressor effect of LSD was very small indeed, whereas the reduction of the baroreceptor component of the COR was quite considerable. In this case, a direct blocking effect of LSD on the synaptic transmission of the baroreceptor afferents must be considered. If such a block developed, a rise in systemic pressure would be expected at the same time. The absence of a rise in pressure could be accounted for by a simultaneous reduction by LSD of central vasomotor tone.

*The Effect of LSD on the Baroreceptor Depressor Reflex.*—The composite nature of the COR limits its usefulness as a test suitable for investigating the effect of drugs upon the baroreceptor pathway. To permit any conclusion to that end, the baroreceptor depressor reflex should be included in the investigation. The latter can be elicited by electrical stimulation of the carotid sinus nerve; this nerve contains fibres arising both from the baro- and chemo-receptors of the carotid bifurcation area. Depending on the anaesthetic and the type of stimulation (Neil *et al.*, 1949), impulses will predominate in either set of fibres, thus giving rise to a baroreceptor depressor or a chemoreceptor pressor response.

LSD failed to inhibit the blood pressure fall produced by electrical stimulation of one sinus nerve. Fig. 4 shows such an experiment per-

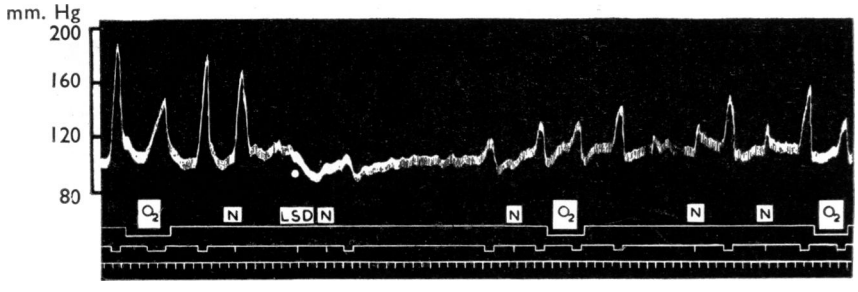


FIG. 3.—Cat, 3.8 kg., chloralose anaesthesia. Both vagi cut, artificial respiration. Tracings from above down: blood pressure; periods of oxygen breathing ($O_2$); long signal indicates carotid occlusion, brief signal indicates injections of 10 $\mu$g. of sebacinyl-bis-choline (N) into the lingual artery and of 200 $\mu$g. of LSD into the lateral ventricle. Time, 30 sec.

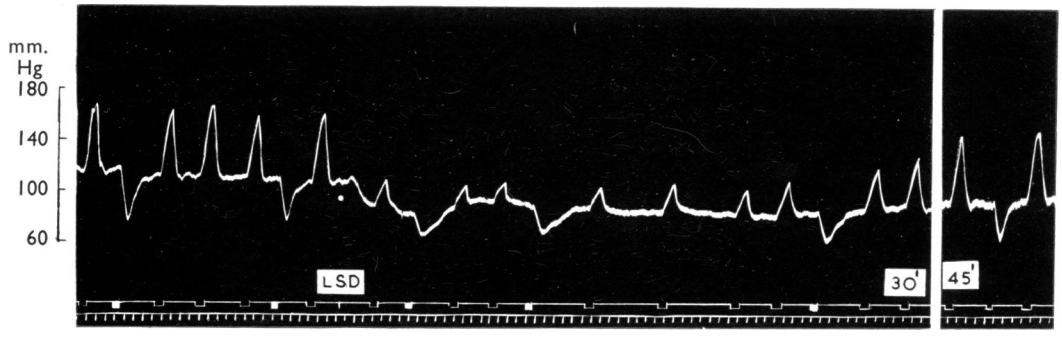


FIG. 4.—Cat, 3 kg., pentobarbitone anaesthesia. Both vagi cut, artificial respiration. Records from above down: blood pressure; long signal indicates carotid occlusion and white blocks indicate stimulation of the left carotid sinus nerve for 20 sec. At the white dot, 150 $\mu$g. of LSD was injected intracerebroventricularly. Time, 30 sec. Times after injection of LSD are given.

formed under pentobarbitone anaesthesia where the baroreceptor depressor reflex was elicited in alternation with the COR. About half the size of the latter was due to chemoreceptor activation (oxygen test is not shown). 150 $\mu$g. of LSD diminished the COR to less than a third of its original height while sinus nerve stimulation was still as effective as before LSD. The over-all depressor response was somewhat reduced owing to the decreased level of systemic pressure, but the same or even a lower minimum pressure was reached during stimulation. From this it appeared that LSD did not interfere with the baroreceptor pathway when it blocked the chemoreceptor reflex.

This conclusion received further support from an experiment in which sinus nerve stimulation elicited the chemoreceptor pressor reflex (Fig. 5). 50 $\mu$g./kg. of LSD was administered, this time by the intravenous route. Shortly after the injection the response to sinus nerve stimulation no longer showed the clear-cut pressure rise but only a series of oscillations suggesting an interplay between reflex pressor and depressor tendencies. Later, these waves were superseded by a distinct depressor effect which increased up to the 25th min. after the injection of LSD. Then it diminished gradually and gave way again to the previous "oscillation" response. After 2 hr. the initial pressor response to sinus nerve stimulation was restored. The effect of noradrenaline, injected intravenously, was not changed throughout the experiment.

The conversion by LSD of the pressor response to stimulation of the sinus nerve into a depressor response suggests that the chemoreceptor impulses which predominated before LSD was given were blocked, and the impulses elicited in baroreceptor fibres during stimulation determined the effect then observed.

When the COR was almost completely inhibited by LSD, it was frequently observed that the pressure dropped below the original level as soon as the clamps were removed from the carotid arteries (see Figs. 3 and 8). This phenomenon was probably nothing more than the carotid depressor reflex set into action by the sudden restoration of

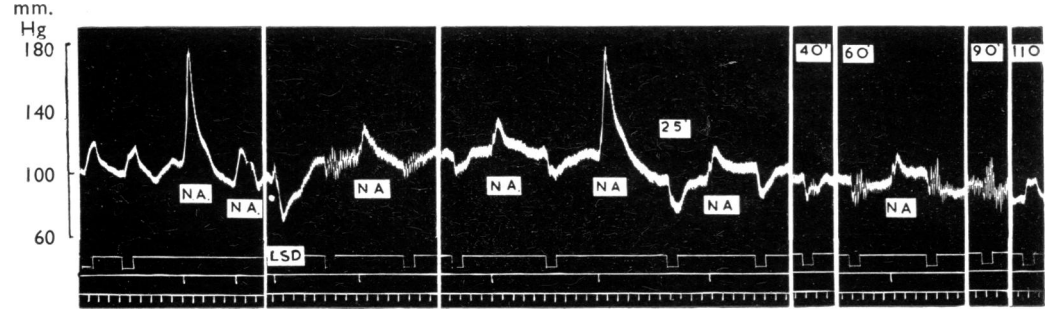


FIG. 5.—Cat, 2.5 kg., chloralose anaesthesia. Both vagi cut, artificial respiration. Tracings from above down: blood pressure; upper signal indicates stimulation of the right carotid sinus nerve; lower signal indicates injection; time, 30 sec. At NA., intravenous injections of 2 and 0.2 $\mu$g. of noradrenaline respectively. LSD, 50 $\mu$g./kg. LSD intravenously. Times from the injection of LSD are shown.

intrasinusal pressure after declamping. The depressor reflex is usually not visible when the COR develops to full size, then being only part of the general return of the raised pressure to its normal level.

*The Site of the Reflex Blocking Effect of LSD.*—LSD blocked various vasopressor reflexes after administration of the drug into the lateral ventricle of the brain. The doses found effective by this route in a given experiment were usually without action on the reflex responses when injected into the femoral vein. Somewhat larger quantities administered by the intravenous route, however, did exert a blocking effect.

No reduction of the effects of nicotine, adrenaline, and noradrenaline was observed during and at the maximum of the reflex blockade produced by LSD by either route. When, however, the intravenous dose of LSD was doubled (namely to about 200 μg./kg.) the pressor action of nicotine was sometimes considerably decreased. There was no inhibition of the actions of adrenaline and noradrenaline even after as much as 500 μg./kg. of LSD intravenously. The response of the nictitating membrane to preganglionic sympathetic stimulation was not affected by injection into the lingual artery of 50 and 100 μg. of LSD, indicating that LSD did not impair transmission through the superior cervical ganglion.

From these findings it can be concluded that the block of vasomotor reflexes by LSD did not involve a blockade of impulse transmission through junctional regions within the peripheral efferent pathway of the reflex.

Further, it was found that intra-arterial injection of 50 or even 100 μg. of LSD to the carotid chemo- and baro-receptors did not alter the size of reflexes arising from these receptors. Thus the peripheral part of the afferent reflex pathway also remained unaffected. All this evidence suggests a central point of attack for the blocking action of LSD on vasomotor reflexes.

In an attempt to determine this site of action more closely, two cats anaesthetized with chloralose were decerebrated by suction at the intercollicular level. It was found that LSD blocked the chemoreceptor pressor reflex after this procedure just as it did before. In two cats decerebrated at the same level anaesthetized with ether and then allowed to rest until the anaesthesia had worn off, LSD failed to exert a blocking effect. It did, however, produce a block with the usual dose, after 20 to 30 mg./kg. of chloralose had been injected. Hence, it appears that the ability of LSD to block vasomotor reflexes by interfering with the central part of the reflex pathway below the intercollicular level depended upon the presence of an anaesthetic such as chloralose.

*The Effect of LSD on Respiratory Reflexes.*—The major physiological significance of the carotid chemoreceptor mechanism lies in its regulatory influence on respiration. A reflex excitation of respiration can be obtained by intra-arterial injections of N or potassium cyanide into the carotid bifurcation. LSD failed to exert a blocking action on this respiratory chemoreceptor reflex.

In Fig. 6 the intracerebroventricular injection of 100 μg. of LSD caused a slowing of respiration; the response to N, however, was unchanged. A further injection of 100 μg. of LSD reduced the frequency and amplitude of the respiratory movements to a level no longer sufficient for adequate oxygenation, but it still permitted distinct although correspondingly lowered responses to N and KCN. The same behaviour was observed when the respiration was stimulated by the breathing of 5% carbon dioxide. Thus LSD, depressing respiratory function as a whole, lacks a selective blocking action on the respiratory chemoreceptor reflex.

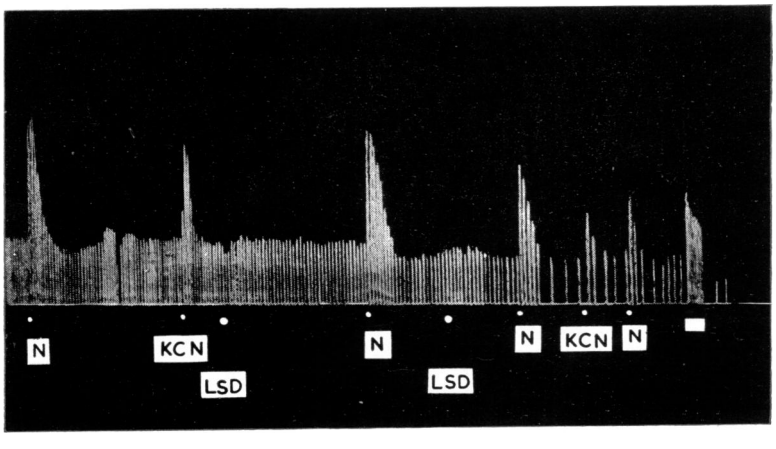


FIG. 6.—Cat, 3.1 kg., chloralose anaesthesia. Both vagi cut. Record of respiration (inspiration only). At white dots, injection into the lingual artery of 8 μg. of sebacinyl-bis-choline at N and 100 μg. of potassium cyanide at KCN. At LSD, intracerebroventricular injections of 150 μg. of LSD. At the white bar, artificial respiration for 30 sec.

*The Effect on Carotid Reflexes of Some Derivatives of LSD and of Other Substances.*—First of all, it was important to find out whether a derivative without the well-known property to induce autonomic and mental changes in man would or would not exhibit a blocking action on reflexes as LSD. The 2-bromo derivative of LSD, BOL-148, has no psychological action (Cerletti and Rothlin, 1955), but it blocked the COR and the pressor reflex elicited by N, and abolished the difference in the height of the COR during air and oxygen breathing respectively. The strength of the action was about half of that of LSD. Lysergic acid pyrrolidide, LPD 824, which also appears to lack mental actions, was also effective on the reflex; the doses required for intracerebroventricular injection were similar to those of 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 effect of the latter by 2 to 5 times whereas the (−)-acetyl lysergic acid diethylamide, ALD 52, did not interfere with reflex responses in doses up to 400 μg. administered intracerebroventricularly.

Dihydroergotamine, another member of the ergot group, was injected into the lateral ventricle; it suppressed the response to chemoreceptor stimulation when given in amounts of at least 300 or 400 μg. The intracerebroventricular injection of 300 μg. of ergotamine (*p*H of the solution was 4) did not yield a clear result.

Von Euler and Schmiterlöw (1944) have shown that ergotamine, injected intravenously in doses of about 100 μg., inhibited selectively the carotid baroreceptor reflex by specifically inhibiting baroreceptor fibre synaptic transmission at the vasomotor centre. In accordance with their finding it was observed that the part of the COR remaining after the chemoreceptor reflex had been blocked by LSD disappeared promptly when ergotamine was injected. At the same time the baroreceptor depressor reflex could no longer be elicited either.

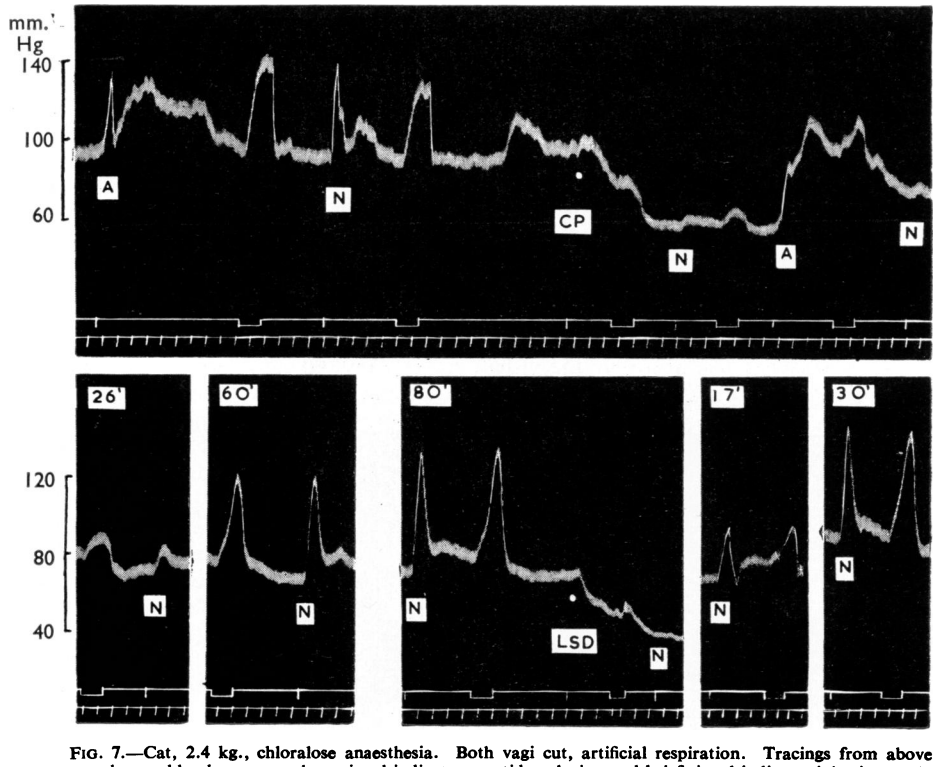


FIG. 7.—Cat, 2.4 kg., chloralose anaesthesia. Both vagi cut, artificial respiration. Tracings from above down: blood pressure; long signal indicates carotid occlusion and brief signal indicates injections. At N, 5 μg. of sebacinyl-bis-choline injected into the lingual artery. At A, 3 μg. of adrenaline intravenously. At CP, intracerebroventricular injection of 200 μg. of chlorpromazine and at LSD of 200 μg. of LSD intracerebroventricularly. Time intervals refer to the intervals elapsing after injections of CP and LSD, respectively. Time, 30 sec.

A number of pharmacologically potent but chemically unrelated substances were also tried in order to determine how common a reflex blocking action was after intracerebroventricular administration of different chemicals. Pentobarbitone sodium, for example, did not interfere with reflex responses even in doses of as much as 6 mg. Mescaline, another drug with psychotropic action, was injected intracerebroventricularly in doses up to 1 mg., but showed none of the actions observed with LSD. Injections of hexamethonium and atropine up to 1 mg. each were without effect. 200 μg. of acetylcholine caused a rise in blood pressure of 40 mm. but did not reduce reflex responses.

LSD is a powerful antagonist to 5-hydroxytryptamine (5-HT) (Gaddum and Hameed, 1954; Ginzel and Kottegoda, 1953). 5-HT was injected into the lateral ventricle in increasing doses; even 1 mg. had no effect whatsoever on carotid reflexes and the blood pressure. Neither did this dose of 5-HT influence the blocking action of LSD, regardless of whether it was administered prior to the injection of LSD or not until the full effect of the latter had developed.

*The Effect of Chlorpromazine on the COR.*—The last substance in this series tried by the intracerebroventricular route was chlorpromazine (CP). CP had been shown to interfere with vasomotor responses (Dasgupta and Werner, 1954). Kalkoff (1955) and Krause and Schmidtke-Ruhnau (1955) have concluded from their experiments that CP blocks carotid baroreceptor reflexes.

It was found that CP suppressed the response to carotid occlusion and chemoreceptor stimulation when injected intracerebroventricularly in doses of the same order as those of LSD. Fig. 7 shows an experiment where 200 μg. of CP caused such a block; the pressor effect of adrenaline injected intravenously was not affected. One hour after the injection of CP the reflex responses were restored to their original size. A subsequent injection of LSD (200 μg. as well) induced a block again, and once more full recovery was obtained, this time ½ hr. after the injection.

When CP was given by the intravenous route in doses of up to 1.5 mg./kg., it failed to block the chemoreceptor pressor reflex elicited by intra-arterial injection of N. In this way it differed from LSD and from the effect of CP given in to the cerebral ventricles. Still higher doses, amounting to 10 mg./kg., reduced the chemoreceptor response to N by one-third only—namely, by the same extent as they reduced the response to noradrenaline. The action of a previously equipotent dose of adrenaline had already been blocked after the first intravenous injection of 250 μg./kg. of CP.

The fall in systemic pressure following the injection of CP was usually greater than that after LSD. As with LSD, an abolition by CP of the chemoreceptor component of the COR was observed. The carotid depressor reflex elicited by electrical stimulation of the carotid sinus nerve was not inhibited by CP when the COR was blocked (Fig. 8). The COR being abolished, a drop in pressure ensued on removing the clamps from the carotid arteries. These findings agree with those obtained with LSD and permit similar conclusions.

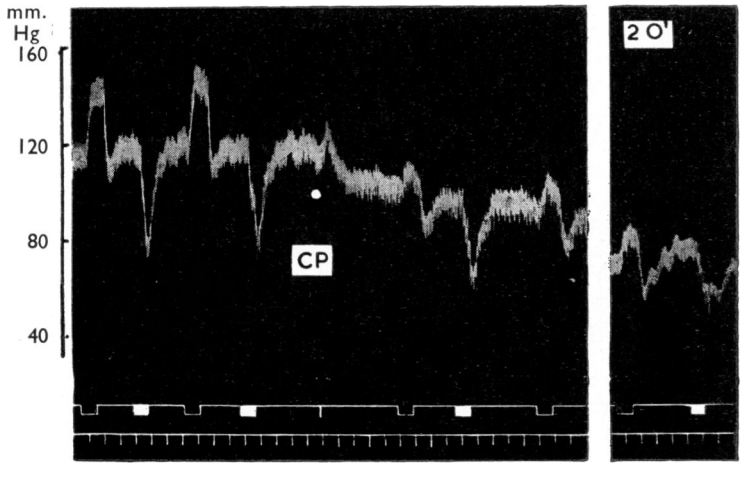


FIG. 8.—Cat, 2.7 kg., chloralose anaesthesia. Both vagi cut, artificial respiration. From above down: blood pressure; long signal indicates carotid occlusion; white bars indicate stimulation of the right carotid sinus nerve; time, 30 sec. At CP, 250 μg. of chlorpromazine was injected intracerebroventricularly.

## Discussion

The symptoms produced in man by ingestion of as little as 0.5 to 1 μg./kg. of LSD include disturbances of autonomic functions such as changes in blood pressure and pulse rate, flushing, sweating, trembling, and cold and heat sensations. Seldom is embarrassment of respiration noted.

In anaesthetized cats, LSD was found to interfere with the homeostatic control of blood

pressure based on the function of the carotid receptors, and with other reflexes influencing circulation. The doses required to exert these effects were at least 100 times greater than those used in man. Moreover, the blocking action on vasomotor reflexes was not limited to LSD and those of its derivatives which elicit autonomic and mental symptoms in man. It is therefore unlikely that the results obtained under these experimental conditions have any bearing on the effects which LSD produces in man.

Neither could a direct correlation be established between the blocking effects of LSD and derivatives, and their ability to antagonize 5-HT as tested on the rat uterus. LPD 824 and LAE 32 possessed only 1/20 and 1/8 respectively of the anti-5-HT action of LSD (Cerletti and Konzett, 1956). LPD 824 was equal to LSD in blocking carotid reflexes, whereas LAE was 2 to 5 times stronger. ALD 52 on the other hand, which exceeds the 5-HT-antagonistic potency of LSD, lacked a blocking effect altogether ; it was injected intracerebroventricularly up to a dose twice as large as the blocking dose of LSD.

This comparison, however, does not permit an answer to the question whether the reflex blockade caused by LSD and other substances may or may not involve a mechanism dependent on 5-HT. One has to take into account that the ability of antagonists to block effects elicited by 5-HT varies with the particular test object used (Cerletti and Konzett, 1956). Further, as in the case of the intracerebroventricular administration, the access of these drugs to the site of their action and thus their actual efficacy is eventually determined by the permeability of the CSF-brain barrier. This factor, however, is not known.

On the other hand, little support is lent to the possibility of 5-HT having a rôle in the function of vasomotor reflexes, by the fact that this substance, even in such an exceedingly high amount as 1 mg., interferes neither with these reflexes nor with the blocking effect of LSD. One is justified in assuming that at least a part of the 5-HT has reached the neuronal substrate underlying this action, since smaller amounts of 5-HT can gain access to some other structures of the brain ; Feldberg and Sherwood (1954) have shown that an injection of 75 to 500 $\mu$g. of 5-HT into the intracerebroventricular space of a conscious cat provokes definite behavioural and autonomic reactions in the animal.

The fall in blood pressure following the intracerebroventricular administration of LSD or CP still occurred after vagotomy and atropine, and must therefore be due to a diminution of central vasomotor activity. This fall in pressure was sometimes very great with a given dose, but the blocking action on the chemoreceptor pressor reflex was not necessarily great at the same time. On the contrary, it was even observed in two experiments, where the systemic pressure fell to a level as low as 40 mm. Hg, that the response to chemoreceptor stimulation was hardly affected at all ; only a second dose abolished the reflex. The other possible extreme encountered was a very weak effect on the blood pressure with a full block of the chemoreceptor response from the outset. Thus, the effect of these drugs on the reflex appears to be clearly distinct from the effect on the discharge from vasomotor areas. This suggests that each effect has a site of action on a nervous structure afferent in respect to the final relay station (medullary vasomotor centre) in which the efferent vasoconstrictor pathway originates. Alternatively, the efferent neurone of the chemoreceptor pressor reflex might be entirely independent of the final common pathway of sympathetic vasomotor activity.

The results of the investigation into the mechanism by which LSD and CP diminish the blood pressure response to carotid occlusion led to some general conclusions. Frequently it is inferred from a simple reduction of the COR by a drug that neurones underlying the baroreceptor reflexes have been affected. It must be stressed, however, that no such conclusion is permissible unless a pure baroreceptor reflex has actually been tested. The COR is a mixed phenomenon whose chemoreceptor component can differ considerably. A diminution of the COR may sometimes solely be accounted for by the abolition of its chemoreceptor component. This was also the major feature in the action of LSD and CP on the COR. The part of the COR based on baroreceptor function depends on the level of systemic pressure at the time and may therefore decrease merely as a consequence of a decrease in pressure caused by the drug under investigation and not by a direct effect of the latter on the baroreceptor pathway.

The action of LSD on the COR is mainly an action on the chemoreceptor reflex. Ergotamine, however, a substance deriving from the same parent compound as LSD, predominately affects the baroreceptor component of the reflex. Thus, two members of one chemical group are able to distinguish by their action between pathways connecting two different types of peripheral receptors, the chemo- and baro-receptors of the carotid sinus, to one central pool, the medullary vasomotor

centre. On the other hand, with regard to the respiratory chemoreceptor reflex which was not selectively blocked by LSD, a pharmacological differentiation seemed also possible between pathways connecting *one* set of peripheral receptors, the carotid chemoreceptors, with two different central sites, the respiratory and the vasomotor centres of the medulla.

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