Discussion Third Symposium: Comparison of abnormal behavioral states induced by psychotropic drugs in animals and man.

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A. CERLETTI

Sandoz Ltd., Basle (Switzerland)

Among the many hundreds of publications on LSD, relatively few have dealt more extensively with the various effects of this drug on the autonomic nervous system. This may be the reason why one of the best reviews of psychopharmacological problems still contains the statement that "one cannot draw any conclusions regarding the central autonomic actions of LSD"[14]. Perhaps even less attention has been paid to the fact that LSD is not only chemically but also pharmacologically closely related to ergot alkaloids. This is true, even though reference has been made several times to the adrenosympatholytic property of ergot compounds when discussing the antiserotonin effect of LSD. It seems to the author that in this particular respect LSD has very little in common with the adrenaline-antagonistic group of peptide ergot alkaloids, whereas in other respects common properties of the ergot pharmacology can easily be discerned also in LSD.

An attempt will therefore be made, to define the position held by LSD within the framework of several well known ergot compounds. Using this general information as a background, the results of comparative studies in humans and animals with 18 amide derivatives of lysergic acid will subsequently be reviewed.

Practically all the effects of the different ergot alkaloids observed *in vitro* and *in vivo* can be classed into one of the following six distinct categories:

1. Uterine contraction	direct action on *smooth muscle* cell	*peripheral* effects
2. Vasoconstriction	direct action on *smooth muscle* cell	*peripheral* effects
3. Serotonin antagonism	interference with *amines* at the receptor side	*peripheral* effects
4. Adrenergic blockade	interference with *amines* at the receptor side	*peripheral* effects
5. Bulbo-medullary effects	stimulation and/or inhibition of *brain stem* substrates	*central* effects
6. Mesodiencephalic effects	stimulation and/or inhibition of *brain stem* substrates	*central* effects

Based on the activity of different ergot compounds, when tested according to these criteria, a spectrum can be designed for each compound, which allows us to estimate at once the relative importance of single activity-components within the

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overall effectiveness of any of these drugs. The Figs. 1, 2 and 3 may serve better than a long comment to explain the procedure. In the case of each compound only a relative scale is used, beginning with the minimal effective dose and ending with the 100 % lethal dose. The position of any single point in one of these "spectra" can therefore not be compared directly, for example in terms of milligrams, with a corresponding point for another derivative. LSD for instance is nearly as potent as ergonovine as far as its action on the uterus is concerned. But in the case of the natural alkaloid, an oxytocic dose of 0.1 mg/kg corresponds to only about 2 % of the LD_{50}, whereas for LSD the same amount represents already more than 30 % of the LD_{50}. The corresponding points in Fig. 3 are therefore differing according to this latter ratio.

An extensive pharmacological analysis of LSD in our laboratory[1-3,6-9,11-13] has shown that this substance can very well be defined pharmacologically in terms of the 6 typical criteria (listed above). Proceeding in this way, the surprising fact emerges that the special feature about LSD is not the appearance of any fundamental new property, but rather a shifting of the relative importance of the various elements already present in the natural amide derivative of lysergic acid, *i.e.* in ergonovine. Similarly the hydrogenated derivatives of natural peptide alkaloids achieve their new pattern of pharmacological activity and of clinical usefulness simply by a different quantitative distribution of the single components. In the case of LSD the action on the higher autonomic centers in the mesodiencephalic area becomes the most prominent part of the spectrum. The same is, however, also found in the spectrum of other ergot compounds, but it enters the picture only when the toxic dose-range is

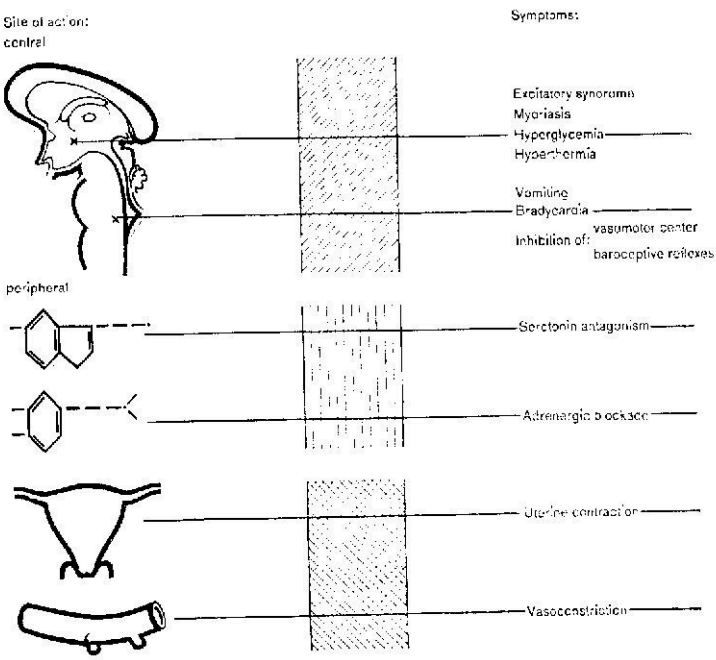

Fig. 1. Ergot pharmacology. The main pharmacological criteria determining the overall activity of ergot compounds.

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approached or reached. In this connection the question might arise whether any of the types of ergot poisoning in older times ought not to be partly attributed to that LSD-like property of natural alkaloids. It is obvious that LSD-like central effects of ergot alkaloids could not occur in the form of more or less isolated phenomena as is the case with regular doses of LSD, but that they were heavily overshadowed by the

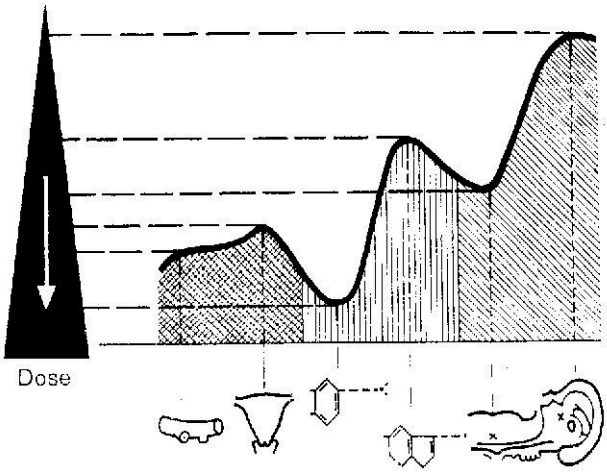

Fig. 2. General design of an activity spectrum.

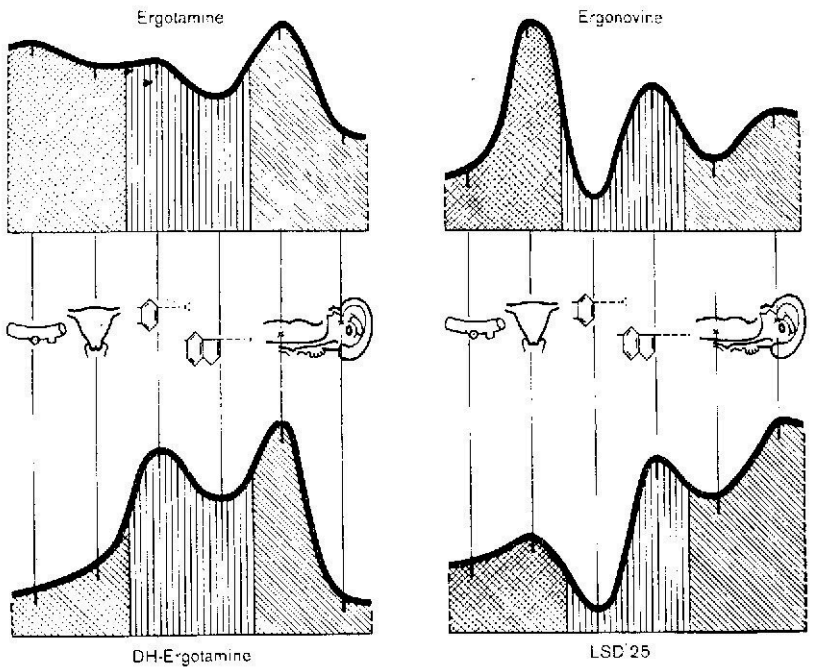

Fig. 3. Activity spectra.

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general intoxication which mostly affected also peripheral structures directly. Anyhow it does not seem absurd to think that such a masked LSD-like syndrome may possibly have occurred hundreds of years before the substance LSD itself existed.

The action of ergot compounds on the more rostral parts of the brain, in animal experiments, gives rise to a number of symptoms mainly in the neurovegetative area (hyperthermia, hyperglycemia, mydriasis, piloerection, tachypnea etc.) and to hyperreflexia as well as to a certain general motor hyperactivity. This whole excitatory syndrome (= E-syndrome) is markedly developed in the case of LSD, but it is also provoked by other drugs belonging to the group of simple amide derivatives of lysergic acid. Since quite a number of such compounds have been studied in the meantime in humans as well, we may endeavour to find a certain correlation between their effect in animal experiments on one hand and their psychic action in man on the other. We selected for such a comparison 18 derivatives which are all closely related to LSD, as shown in Fig. 4. For the quantitative classification of this series of compounds in terms of LSD-like activity in man, the oral dose necessary to produce effects of the same intensity as 1 to 1.5 μg/kg LSD, has been determined. The values for the relative activity estimated in this way, which form the basis for the comparative survey presented in Fig. 5, are mostly results obtained by ISBELL[5]. As can be seen in Fig. 5, some psychotogenic activity is present in different LSD-derivatives with variations of the amide group. As soon as chemical changes are induced on the ring system, the three chemical groups of examples (groups B, C, D in Fig. 4) show a certain systematic modification of their effectiveness: all changes of the steric configuration typical for *d*-lysergic acid lead to a practically complete loss of specific effects not only in man, but also in animals and in tests *in vitro*. The loss of the C_9–C_{10} double bond by hydrogenation or hydration (dihydro-LSD and Lumi-LSD respectively) abolishes in any case the psychotogenic effect. Pharmacologically this type of derivatives is, however,

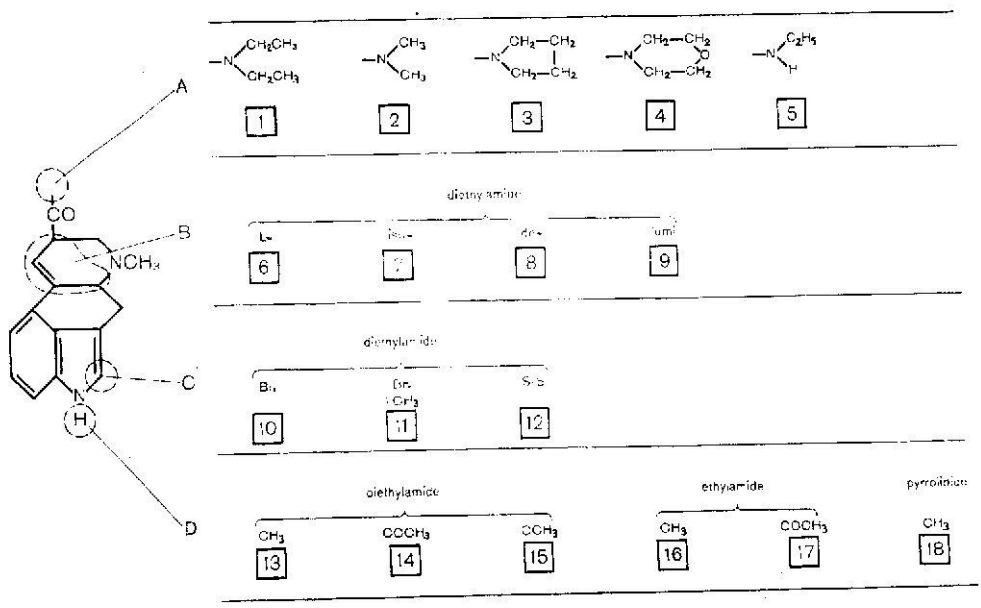

Fig. 4.

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not as inactive as the isomers, except that, as in the case of the latter, the E-syndrome completely disappears also. On the right side of Fig. 5, the relative values for the antiserotonin and pyretogenic activity of the 18 compounds are also shown on a logarithmic

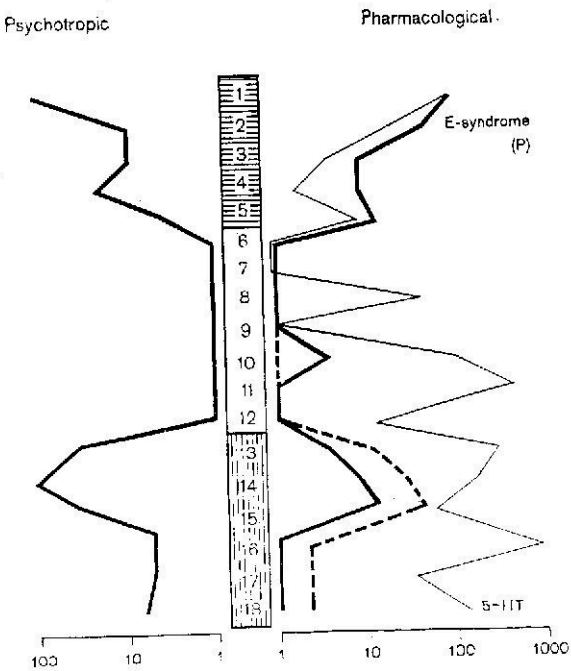

Fig. 5. Correlation between the activity of lysergic acid derivatives.

scale, and it can be seen that dihydro-LSD still maintains a considerable antiserotonin potency in spite of having completely lost the effects constituting the E-syndrome. It is, however, remarkable to note that dihydro-LSD shows other distinct effects on the CNS, mainly a high stimulation of respiration combined with a marked convulsive property, being in these respects up to 10 times more potent than metrazol for example. In a certain way, this situation is similar with the compounds listed as group B in Fig. 4. They all have in common that position 2 of the ring system is no longer free. Due to this fact a practically complete disappearance of the psychotogenic effect in man and of the E-syndrome in animals can be noticed, although several other pharmacological properties still persist. It was therefore interesting to make a similar comparison with derivatives like those in group D, which all have a substituent in position 1, *i.e.* on the indole nitrogen of lysergic acid. Chemical modification of this type has resulted in extremely interesting derivatives, not only in the group of low molecular amide-derivatives of lysergic acid but also in the group of natural and hydrogenated ergot alkaloids. Methylation of the indole nitrogen is especially effective in diminishing or even eliminating certain central actions of the ergot compounds, as for example vomiting. In the case of LSD and closely related derivatives, the 1-substitution diminishes especially the pyretogenic effect, whereas other symptoms of central autonomic stimulation are not affected and some may even be enhanced. If

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therefore, not a single symptom (pyretogenic effect), but rather the whole reaction described above as E-syndrome is used as the guiding principle for the comparison, the group of 1-substituted derivatives (compounds 13–18) confirms the existence of a certain correlation between this pharmacological character of a substance and its psychic activity in man. It is impossible to evaluate the whole E-syndrome quantitatively in a way as can be easily done with the pyretogenic action. For this reason the heavy line on the right side of Fig. 5 representing the measured values of pyretogenic activity is supplemented by a broken line for the cases where due to reduced pyrogenicity, it is necessary to rely more on the estimated overall intensity of the E-syndrome. For the first 12 compounds, no such correction is necessary because the pyretogenic activity and the degree of total excitatory symptoms vary in parallel. The only slight exception is the finding that brom-LSD (compound 10) in large doses causes a very small temperature increase without any other excitatory symptoms, or even reversing them, causing a certain sedative effect.

We have also included in Fig. 5 the relative antiserotonin activity of the 18 compounds, not so much for stressing again the lack of correlation between this pharmacological parameter and the findings in human experiments, but rather as a contrast with the neat congruence which can be found when another hypothesis is tested. The formulation of such a hypothesis is the same as that of the general conclusion derived from our comparative study of lysergic acid derivatives, namely that a certain pattern of central autonomic stimulation is one of the major factors determining the psychotogenic quality of LSD and LSD-like compounds. An essentially identical hypothesis had already been put forward some years ago[4], but it had been based mainly on the analysis of centrally mediated LSD effects on the sympathetic system. The pharmacological and clinical study of the LSD-congeners confirms that hypothesis on a more general basis. Concerning the more intimate connections between psychic and autonomic functions, HESS published a paper[4] in 1925, which unfortunately has not yet been given the attention it merits, probably due to the fact that the more dramatic developments of psychopharmacology started only 20 years later. Reading the ultimate conclusions reached by HESS, without knowing the date when that statement was made, one could readily assume that it referred also to LSD. We cannot find a more apt conclusion expressing the gist of the study which we have presented than by quoting the words of HESS: "Es sind ferner die Umstimmungen der psychischen Aktivität durch gewisse Reizstoffe zu nennen, auf welche einzelne Abschnitte des vegetativen Nervensystems elektiv empfindlich sind. Die Resonanz, welche der Steuerungsapparat der psychischen Aktivität – in Folge seiner Zugehörigkeit zum vegetativen Nervensystem – auf vegetative Reizstoffe zeigt, lässt Symptome auftreten, welche im Kleide sog. "zentraler Wirkungen", erscheinen. Analoge Folgerungen aus unsern Auffassungen über den regulatorischen Einfluss des vegetativen Nervensystemes auf die Organe psychischer Funktion ziehen wir in bezug auf die Pathogenese von Geisteskrankheiten. Dabei erkennen wir die Möglichkeit, dass der gleiche Apparat, durch dessen Funktion die Harmonie zwischen vegetativen und animalen Bedürfnissen im Gebiete psychischer Tätigkeit zustande kommt, zum Überträger eines Störungsfaktors wird. Er reisst das an sich gesunde Organ psychischer Tätigkeit mit in den Zustand krankhafter Funktionsäusserung hinein *und die im Bereiche des vegetativen Nerven-systemes liegende Krankheitsursache wird zur Ursache einer Störung der psychischen Funktion.*"

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