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STUDIORUM PROGRESSUS

A Central Nervous System Effect of a Non-Hallucinatory Lysergic Acid Derivative

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The effect of serotonin (5-HT) on smooth muscle and other peripheral sites is antagonized by certain lysergic acid derivatives, among them D-lysergic acid diethylamide (LSE-25) and 2-brom-D-lysergic acid diethylamide (BOL-148)[1]. MARRAZZI and HART[2] have demonstrated a central synaptic inhibitory action of 5-HT in small doses, indicating a possible role for 5-HT in regulating impulse transmission. The competition between 5-HT and the lysergic acid derivatives was proposed as the mechanism underlying the central nervous system actions of LSD-25, a powerful hallucinatory agent[3]. However, BOL-148 has no such hallucinatory ability[4] although it was shown to be as potent if not a more potent antagonist than LSD-25 of the actions of 5-HT peripherally. It occurred to us that BOL-148 might be competing with 5-HT at the synapse, and that it is possibly just as potent an inhibitor of central synaptic transmission as 5-HT. Therefore, if 5-HT, the *normal* inhibitor, is replaced by an equally potent inhibitor, there should be no marked deviation from the normal situation, and no hallucinatory effect. We felt it to be of interest to investigate the effect of BOL-148 on central synaptic transmission. A transcallosal evoked potential method similar to the MARRAZZI and HART[2] modification of the CURTIS and BARD[5] method was used.

Fig. 1. — Films of the oscilloscope face demonstrating the heights of the post-synaptic potentials before, during, and after the inhibitory effect of 200 mcg/kg of BOL-148 injected into the carotid artery ipsilateral with the recording electrodes.

When BOL-148 is injected into the carotid artery of a cat anesthetized with pentobarbital, it produces a marked inhibition of the evoked negative postsynaptic response in the monosynaptic corticocortical (trans-callosal) pathway as represented in Figure 1. This is interpreted as a depression of synaptic transmission in this system[6]. The inhibition occurs approximately thirty seconds after the injection of 100–500 mcg per kg of BOL-148. When the negative post-synaptic potential has returned to control level, it has been our experience in several experiments, that the synaptic transmission is temporarily unresponsive to previously-depressing doses of 5-HT or LSD-25. Figure 2 demonstrates the reduction of 5-HT action after the injection of BOL-148. The antagonism to the synaptic inhibitory effects of these compounds after BOL-148 injection may last as long as forty-five minutes. This effect is being studied at present and will be reported upon more fully in the future.

The actions of BOL-148 in central synapses and on peripheral organs are apparently similar. At both sites of action, BOL-148 blocks the effect of 5-HT. 5-HT exhibits different actions at the two sites, stimulating the peripheral organs in question[1] while inhibiting central synaptic transmission[2]. BOL-148 blocks both 5-HT stimulation of peripheral organs[6] and apparently, 5-HT inhibition of central synaptic transmission. The possible interaction between 5-HT and LSD-25 in this system is also under investigation, although it has been claimed that LSD-25 does not interact with 5-HT in central synapses[7].

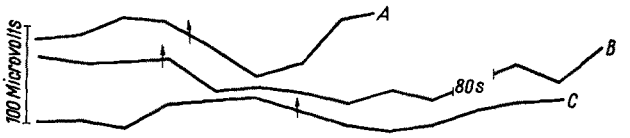

Fig. 2.—These curves are obtained by plotting the mean heights of each series of ten successive post-synaptic potentials (P.S.P.'s) against the mean times for these P.S.P.'s.

It is difficult to state specifically which of the synaptic inhibitors under discussion (5-HT, LSD-25 or BOL-148) is most powerful in this regard, because of permeability, breakdown, affinity for receptors and other factors. However, from the data obtained by studying the effects of the lysergic acid derivatives and their competition with 5-HT on peripheral organs it would seem that BOL-148 is a more potent competitor than LSD-25[8]. BOL-148 and serotonin may be equally potent inhibitors of synaptic transmission, so that replacement of a normally-occurring inhibitor, serotonin, with one of possibly equal potency, Bol-148, produces no great change from the normal and hence, no hallucinatory action. We realize that this speculation is an extreme oversimplification.

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Zusammenfassung

Ähnlich wie Serotonin und LSD-25 vermindert BOL-148, ein Lysergsäurederivat, das keine Halluzinationen erzeugt, die durch den Balken fortgeleiteten, postsynaptischen Potentiale. Vorbehandlung mit BOL-148 macht das Versuchstier für ungefähr eine Stunde unempfindlich gegen Serotonin. BOL-148 blockiert anscheinend im Zentralnervensystem wie auch in der Peripherie den Serotonineffekt. Es wird versucht, zu erklären, weshalb diese Droge keine Halluzinationen bewirkt.

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