LSD 316

Proc.Soc.Exper.Biol.Med., N.Y. 94, 433 (1957).

LSD-Like Effects Elicited by Reserpine in Rabbits Pretreated With Iproniazid.* (22968)

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Previous findings have led us to postulate that the sedative and parasympathomimetic effects of reserpine are mediated through serotonin, and that serotonin may be a chemical transmitter in the parasympathetic division of the central autonomic nervous system(1,2). These concepts are based in part on the findings that both serotonin and reserpine induce sedative effects in mice and potentiate by a central mechanism the action of certain hypnotics, the potentiation by either substance being antagonized by pretreatment with lysergic acid diethylamide (LSD); and that the prolonged effects of reserpine are associated with a persistent impairment of the capacity of the body to maintain serotonin in the bound form which normally protects the amine from the action of the active enzyme, monoamine oxidase. As a consequence, serotonin is liberated and rapidly metabolized, but as the enzyme in brain responsible for formation of serotonin remains unimpaired, the possibility has been considered that reserpine administration results in a persistent flow of serotonin from cells which have lost part of their capacity for storing the indole. The total level of serotonin is low, as would be expected because free serotonin is rapidly metabolized by monoamine oxidase, but the free amine might stimulate the central parasympathetic centers, thus producing the signs typical of reserpine.

The present paper describes studies which demonstrate that when reserpine is administered to rabbits pretreated with the monoamine oxidase inhibitor, iproniazid, the animals, instead of showing sedative and parasympathomimetic responses typical of reserpine, display instead the excitatory and sympathomimetic effects typical of lysergic acid diethylamide (LSD). Furthermore, the concentration of serotonin in brain, which declines rapidly after the administration of reserpine alone, now remains at its normal level.

Methods. Male albino rabbits were given various drugs intravenously and were killed by intravenous injection of air one hour after administration of the last drug. Serotonin in brain was assayed by the fluorometric procedure described by Bogdanski *et al.*(3).

Results. Five rabbits given reserpine (5 mg kg) demonstrated typical responses to the drug including deep sedation and parasympathomimetic effects including miosis and relaxation of nictitating membrane. Five animals pretreated with 100 mg kg of iproniazid and 2 hours later given 5 mg kg of reserpine showed no parasympathomimetic effects, but rather displayed gross excitation, mydriasis, exophthalmus, piloerection, and other sympathomimetic effects. Animals given iproniazid alone, displayed no obvious signs.

It seemed possible that the sympathomimetic effects observed following the administration of reserpine to iproniazid-treated rabbits were caused by the drug combination rather than by serotonin which had been released by reserpine and protected by iproniazid from the action of monoamine oxidase. This possibility was investigated with another series of 5 rabbits in which the order of drug administration was reversed; that is, the ani-

* Presented in part before the American Soc. for Pharmacol. and Exp. Therap., Iowa City, Sept. 1955.

TABLE I. Effect of Iproniazid on Concentration of Serotonin in Brains of Normal and Reserpine-Treated Animals.

Rabbits were given reserpine (5 mg/kg) intrav. Iproniazid (100 mg/kg) was admin. intrav. 2 hr before or after reserpine. Animals were sacrificed one hr after admin. of the last drug. Each value represents a single animal.

Drugs admin.	Brain serotonin, μg/g	Effect
None	.51, .53, .62, .54, .55	
Iproniazid	.60, .67, .63, .62	None
Reserpine	.08, .12, .10, .12, .08	Sedation
Iproniazid followed by reserpine	.40, .44, .72, .56, .55	Excitement
Reserpine followed by iproniazid	.18, .16, .10, .11, .06	Sedation

mals were given reserpine followed 2 hours later by iproniazid. All of these animals were sedated and showed parasympathomimetic signs associated with reserpine administration.

In Table I are compared the serotonin levels in brains of normal animals and of animals given the various drugs. The serotonin level in whole brains of animals given reserpine alone declined from about 0.55 to about 0.1 μg g of tissue. Iproniazid alone had only a slight effect on the concentration of serotonin in the time period of these experiments. Brains of animals given iproniazid followed by reserpine showed about the same concentration of serotonin as did those of normals. On the other hand, animals in which reserpine was given 2 hours before iproniazid showed a marked decline in brain serotonin.

The pharmacologic effects obtained when reserpine was administered in the presence of iproniazid were compared with the effects that followed administration of 0.1 to 0.2 mg/kg of LSD which has been shown to have no serotonin-releasing activity(4). Five animals given the hallucinogenic compound exhibited sympathomimetic responses including excitation, mydriasis, exophthalmus, and piloerection that could not be distinguished from those observed following administration of reserpine to animals pretreated with iproniazid. The effects induced by LSD could be overcome by the administration of either chlorpromazine (5 mg/kg) or reserpine (5 mg/kg).

The effects of reserpine and chlorpromazine were also determined in 6 animals grossly excited by administration of iproniazid followed by reserpine. Administration to 3 of these animals of another dose of 5 mg/kg of reserpine failed to reverse the excitation. On the other hand, when 5 mg/kg of chlorpromazine was given to the other 3 animals they became rapidly sedated.

The actions of the 2 tranquilizing agents were also compared in rabbits with an excess of free serotonin in the brain produced by the intravenous administration of 100 mg/kg of 5-hydroxytryptophan. As shown by Bogdanski *et al.*, this compound rapidly penetrates brain where it is decarboxylated to form serotonin, and, after large doses, induces excitement and sympathomimetic effects during the period that serotonin is being formed. Administration of 5 mg/kg of reserpine to rabbits pretreated with 5-hydroxytryptophan failed to reverse the excitation or the sympathomimetic effects but these signs were quickly reversed by chlorpromazine.

Discussion. Administration of reserpine to rabbits pretreated with iproniazid, an inhibitor of serotonin metabolism, causes excitatory and sympathomimetic effects typical of LSD, rather than sedation and parasympathetic predominance seen when reserpine is given alone. Furthermore, reserpine in the presence of iproniazid does not cause the precipitous decline in brain serotonin level seen after administration of reserpine alone. The reversal of the effects of reserpine is not due simply to the combination of drugs, for changing the order of administration results in the usual pharmacologic effects of reserpine and the usual decline in brain serotonin.

Excitation and other LSD-like responses can also be induced in animals by the administration of high doses of 5-hydroxytryptophan, which enters the brain and is there decarboxylated to form considerable amounts of serotonin. The effects of 5-hydroxytryptophan have been shown to be especially pronounced when the destruction of serotonin has been blocked by iproniazid. Thus, it is possible that the bizarre effects of the combination of iproniazid and reserpine are due to serotonin which has been changed by

reserpine from a bound to a free form but which is now protected from degradation by the presence of iproniazid.

It would appear that the usual parasympathomimetic effects of reserpine are associated with a low concentration of free serotonin in brain, whereas sympathetic predominance is associated with a high concentration of the free indole. This apparent difference in the behavior of serotonin, depending on whether it is present in low or in high concentration, is reminiscent of the behavior of acetylcholine, which in high concentration blocks its own action at peripheral ganglia(5). The findings with serotonin are not inconsistent with the concept that serotonin functions as a neurohumoral agent in the parasympathetic division of the central autonomic system. The blockade of central parasympathetic centers could unmask the antagonistic sympathetic centers and result in sympathetic predominance.

An important observation is that reserpine can overcome the excitation and sympathetic predominance induced by LSD but does not block similar responses resulting from a high concentration of free serotonin in brain, whether the free serotonin is produced by administration of its precursor, 5-hydroxytryptophan, or by the combination of iproniazid and reserpine. In contrast, chlorpromazine, which does not release brain serotonin (4), readily reverses the effects of both LSD and a high concentration of free serotonin, suggesting that although the two tranquilizing agents induce a number of similar pharmacologic responses, they do so by different mechanisms. It is possible that chlorpromazine produces its pharmacologic effects by direct blockade of central sympathetic centers.

Summary. 1. Administration of reserpine to rabbits pretreated with the monoamine oxidase inhibitor, iproniazid, causes excitation and sympathomimetic effects similar to those observed after administration of LSD or high doses of 5-hydroxytryptophan. These effects are associated with the presence of a high concentration of free serotonin in the brain. The observations are consistent with the concept that serotonin is normally bound in an inactive form which serves as the precursor form of a neurohumoral agent. 2. Although both chlorpromazine and reserpine reverse the effects of LSD, only chlorpromazine blocks the effects of free serotonin which result from administration of 5-hydroxytryptophan or the combination of iproniazid and reserpine. This suggests that the two tranquilizing drugs act by different mechanisms.

Iproniazid (Marsilid) was kindly supplied by Hoffmann-LaRoche; reserpine phosphate by Ciba Pharmaceutical Products, and lysergic acid diethylamide (LSD) by Sandoz Laboratories.

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Received December 4, 1956. P.S.E.B.M., 1957, v94.