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Behavioral Studies on LEK-8804, a New Ergoline Derivative With Potent 5-HT_{1A} Receptor Agonist and 5-HT_2 Receptor Antagonist Activity

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KRISCH, I. AND B. BOLE-VUNDUK. *Behavioral studies on LEK-8804, a new ergoline derivative with potent 5-HT_{1A} receptor agonist and 5-HT_2 receptor antagonist activity.* PHARMACOL BIOCHEM BEHAV 47(2) 301–305, 1994.—The 5-HT_{1A} receptor-mediated tail flick response in rats and the 5-HT_2 receptor-mediated head twitch response in mice were used to study the functional activity of a new ergoline derivative, 9,10-didehydro-*N*-(2-propynyl)-6-methylergoline-8β-carboxamide (LEK-8804). LEK-8804 dose-dependently elicited spontaneous tail flicks in rats, indicating a full 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) agonist activity. This effect was very similar to that produced by the selective 5-HT_{1A} agonist 8-OH-DPAT, both in terms of potency and time-effect relationship, and was blocked by the selective 5-HT_{1A} antagonist NAN-190. In contrast, LEK-8804 by itself failed to produce head twitches in mice but dose-dependently inhibited the 5-hydroxytryptophan (5-HTP)-induced behavior. The inhibitory effect of LEK-8804 upon 5-HTP-induced head twitches was not attenuated by the selective 5-HT_{1A} antagonist NAN-190. This indicates that probably not the agonist action on 5-HT_{1A} receptors but instead the antagonism on 5-HT_2 receptors was involved in the inhibition of head twitch response. It is suggested that LEK-8804 is a potent full 5-HT_{1A} receptor agonist with possible 5-HT_2 receptor antagonist properties.

Tail flick Head twitch 5-HT_{1A} receptor 5-HT_2 receptor LEK-8804 8-OH-DPAT NAN-190

IT is now well established that the physiological effects of serotonin (5-hydroxytryptamine [5-HT]) in the central nervous system and in peripheral tissues are mediated through different types of receptors. At present, four main classes of 5-HT receptors have been identified: 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4 (5,16,24). The 5-HT_1 receptor group can be subdivided into at least four distinct subtypes, designated as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} (17,34). There is no strong evidence for multiple division of 5-HT_2 receptors (29,31), although it is now clear that the 5-HT_{1C} receptors are more closely related to the 5-HT_2 receptors than other 5-HT_1 receptors in terms of molecular structure, biochemistry, and pharmacological profile for numerous classes of compounds (36,38). Subtypes for 5-HT_3 receptors have been proposed (39) which appear to show primarily a species-dependent distribution (9,24,26). Recently described 5-HT_4 receptors still await more precise characterisation, although new data are accumulating very rapidly (2,16). The present list of 5-HT receptors is very probably not complete. The wide application of molecular biological and radioligand binding techniques now indicate that additional 5-HT receptor subtypes may also exist, yet functional correlates of these receptors still have to be defined (30,37,38,44).

Many agents have been developed that show some degree of selectivity for a particular population or populations of 5-HT receptors. A greater success in this respect has been achieved in the case of 5-HT_{1A} receptor agonists and 5-$HT_{2/1C}$ and 5-HT_3 receptor antagonists (12,14,31). These new drug tools have enabled an improvement in understanding of some aspects of neurochemical basis of the central nervous system functioning. Furthermore, many of them are either in use or being investigated for use as therapeutic drugs for psychiatric disorders. Among them, selective 5-HT_{1A} agonists are currently considered to represent new anxiolytic and antidepressive drugs (6,10,25). Concerning the other 5-HT receptor ligands, some evidence has been reported which suggests that selective 5-$HT_{2/1C}$ antagonists may also be useful as treatments for anxiety and depression (6,10,25).

This report describes the results of the functional evaluation of the new ergoline derivative: 9,10-didehydro-*N*-(2-propy-

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nyl)-6-methylergoline-8β-carboxamide (LEK-8804) (Fig. 1). LEK-8804 showed high in vitro affinity for 5-HT_{1A} and 5-HT_2 receptors and moderate affinity for 5-HT_{1C} receptors in radioligand binding studies with respective K_i values of 0.6, 15, and 80 nM (Teitler, unpublished data). Activity of the compound has been studied in two behavioral models: spontaneous tail flick response in rats and head twitch response in mice, which are considered to represent the activation of 5-HT_{1A} (32,33) and 5-HT_2 receptors (18,43), respectively.

MATERIALS AND METHODS

Animals

Male Han : WIST rats weighing 200–250 g and male Han : NMRI mice weighing 18–25 g were used. They were housed in groups on a natural day-night cycle with free access to food and water at a room temperature of 20 ± 1°C. Experiments were done in the spring, which means that the animals were exposed to daylight from approximately 0500 to 2100. All behavioral studies were performed between 0900 and 1300 in a quiet, artificially illuminated room at a temperature of 23 ± 1°C. The animals were used only once.

Spontaneous Tail Flick Response in Rats

Spontaneous tail flicks, which are tail flicks in the absence of extraneous stimulation, were recorded as recently described by Millan et al. (32). Rats were gently restrained in horizontal transparent plastic cylinders with the tail hanging freely. One spontaneous tail flick was defined as an elevation of the tail to a level higher than that of the body axis. For an examination of the ability of LEK-8804 to induce spontaneous tail flicks, different groups of rats were SC injected with different doses (mg/kg; 0.16, n = 10; 0.31, n = 10; 0.63, n = 8) of the compound or the vehicle (distilled water, n = 6) and immediately afterwards placed in the cylinders. Spontaneous tail flicks were then recorded in 5-min intervals over a period from 5 to 40 min postinjection. The selective 5-HT_{1A} agonist 8-OH-DPAT (mg/kg, SC; 0.16, n = 7; 0.31, n = 8; 0.63, n = 10; 1.25, n = 8; 2.5, n = 17) was tested for comparison (33). The dose-response relationships were constructed for the observation interval from 10 to 15 min postinjection. In order to confirm that LEK-8804-induced spontaneous tail flicks were 5-HT_{1A} receptor mediated, a group of eight rats was injected with the selective 5-HT_{1A} antagonist NAN-190 (13) (0.16 mg/kg, SC) 30 min prior to injection of LEK-8804 (0.63 mg/kg, SC), and the same procedure was used as described above. A group of eight rats treated with vehicle instead of NAN-190 was used for comparison.

Head Twitch Response in Mice

A modification of the method of Handley and Singh (21) was used. Mice from the same stock cage were placed in small sawdust-lined transparent plastic cages (6 × 15 × 14 cm) in groups of three 10 min prior to treatment. One mouse was present in the cage through the experiment but received no further treatment. This mouse was included only because head twitching is reduced when there are only one to two mice per cage (3). Head twitches were identified as rapid lateral rotations of the head similar to pinna reflex (7). To see whether LEK-8804 itself could induce head twitch response, different groups of mice were injected IP with different doses of the compound (0.25, 1, and 4 mg/kg, six mice in each group). Two animals at the same time were observed for 30 min following LEK-8804 injection.

For examination of the effects of LEK-8804 on 5-hydroxytryptophan (5-HTP)-induced head twitches, a pair of mice were injected SC with carbidopa (9 mg/kg) and 15 min later IP with 5-HTP (300 mg/kg). LEK-8804 (0.078–5 mg/kg, IP) was injected simultaneously with carbidopa. One mouse from each pair received the test compound and the other the injection vehicle. Twitches from the two mice were counted in parallel for 5 min starting 30 min post-5-HTP. Head twitch frequency for a test mouse was recorded as the percentage of its paired vehicle-treated control. Nine pairs of mice at each dose level were observed to determine the ID_{50} value, which was defined as the dose of LEK-8804 producing a 50% inhibition relative to 5-HTP/vehicle-treated controls. To determine the possible contribution of 5-HT_{1A} agonist properties of LEK-8804 in inhibition of the head twitch response, the same procedure was used as described above, except that the selective 5-HT_{1A} antagonist NAN-190 (0.16 mg/kg) was mixed with LEK-8804 solutions. The ID_{50} value was not calculated from these experiments. To determine if NAN-190 at the dose of 0.16 mg/kg could influence the 5-HTP-induced head twitches by itself, the responses of nine mice treated with NAN-190 were compared to the responses of their paired controls treated with vehicle. The same experimental procedure as described for LEK-8804 was used for this purpose.

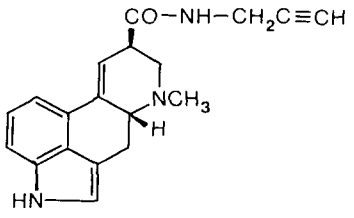

FIG. 1. Chemical structure of LEK-8804.

Drugs and Solutions

The drugs were obtained from the following sources: (±)-8-hydroxy-2-(di-*n*-propylamino)-tetralin hydrobromide (8-OH-DPAT), Research Biochemicals, Inc. (Natick, MA); 1-(2-methoxyphenyl)-4-(4-phthalimidobutyl)-piperazine hydrobromide (NAN-190), Cookson Chemicals Ltd (Southampton, UK); (−)-5-hydroxytryptophan (L-5-HTP), Aldrich-Chemie (Steinheim, Germany); and carbidopa, Merck (Darmstadt, Germany). LEK-8804 tartrate was synthesised at LEK Pharmaceutical & Chemical Co. (Ljubljana, Slovenia). 8-OH-DPAT, NAN-190, and LEK-8804 were dissolved in distilled water, and 5-HTP and carbidopa were dissolved in saline (0.9% w/v NaCl solution). All drugs except 5-HTP were given at a volume of 1 ml/kg to rats and at a volume of 10 ml/kg to mice; 5-HTP was given at a volume of 20 ml/kg. Doses of drugs refer to the weight of the free base.

Statistical Analysis

Dose-response relationships were analysed by one-way analysis of variance (ANOVA) followed by Newman-Keuls test. Comparisons of values of two separate groups of animals were performed using Student's two-tailed t test. The influence of NAN-190 upon the dose-response relationship for the inhibition of 5-HTP-induced head twitches by LEK-8804 was analysed by two-way ANOVA (repeated measures on second factor). The ID_{50} value for LEK-8804 was calculated by logarithm regression analysis. A p value of 0.05 or less was required for

values to be considered significant. Calculations were made using the statistical package PHARM/PCS version 4.2 (42).

RESULTS

Figure 2 shows that both LEK-8804 and 8-OH-DPAT potently elicited spontaneous tail flicks in rats. The number of tail flicks varied considerably between subjects. Therefore, the effects of compounds did not reach significant differences ($p < 0.05$, Newman-Keuls test) from the values of the vehicle-treated control group up to the doses of 0.63 and 1.25 mg/kg for LEK-8804 and 8-OH-DPAT, respectively. The time-effect relationships of both compounds were very similar. The peak time of action of both compounds was 10–15 min postinjection, and the induced response persisted up to 40 min. The induction of the response by LEK-8804 at the highest dose tested (0.63 mg/kg) was completely blocked by the selective 5-HT_{1A} antagonist NAN-190 (0.16 mg/kg) (Fig. 3).

At the doses employed, LEK-8804 by itself did not elicit the head twitch behavior in mice (data not shown). The head twitch response induced by administration of carbidopa followed by 5-HTP was inhibited in a dose-dependent manner by LEK-8804, with an ID_{50} of 0.74 mg/kg (95% confidence limit 0.14–1.34 mg/kg). The 5-HT_{1A} receptor antagonist NAN-190 at the dose of 0.16 mg/kg induced no significant change in the 5-HTP-induced head twitch response ($p > 0.05$, Student's t test, not shown), and neither did it influence the inhibitory effect of LEK-8804 upon the head twitches induced by 5-HTP (Fig. 4).

DISCUSSION

The present results demonstrate that LEK-8804, a new ergoline derivative with high in vitro affinity for 5-HT_{1A} receptors, potently induces spontaneous tail flicks in rats. It may therefore act as a postsynaptic 5-HT_{1A} agonist. According to Millan et al. (33), spontaneous tail flicks in rats can be induced by high efficacy postsynaptic 5-HT_{1A} receptor agonists such as, for example, 8-OH-DPAT. In distinction, partial postsynaptic 5-HT_{1A} receptor agonists, agonists acting at other 5-HT receptors, antagonists at various 5-HT receptors, and numerous other receptor-acting drugs, including α_1-adrenoceptor ag-

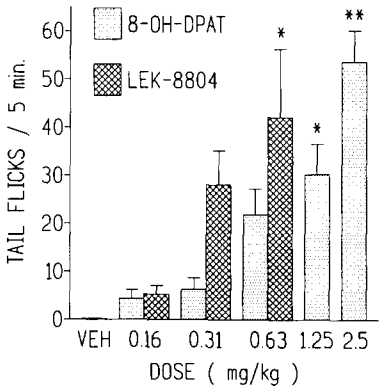

FIG. 2. Induction of spontaneous tail flicks by 8-OH-DPAT and LEK-8804 in rats. Spontaneous tail flicks were counted over a 5-min period, starting 10 min after SC injection. Stars indicate significance of differences to vehicle (VEH, distilled water) in Newman-Keuls test (*$p < 0.05$, **$p < 0.01$) after one-way ANOVA. 8-OH-DPAT, $F(5, 50) = 14.15$, $p < 0.01$; LEK-8804, $F(3, 30) = 5.65$, $p < 0.01$. Bars show means ± SE (n = 6–17 per dose).

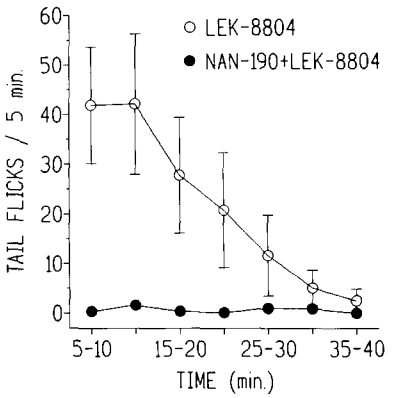

FIG. 3. Time course of spontaneous tail flicks induced by LEK-8804 in the vehicle (○) or NAN-190 (●) pretreated rats. Each rat was SC pretreated with vehicle (VEH, distilled water) or NAN-190 (0.16 mg/kg) 30 min before SC administration of LEK-8804 (0.63 mg/kg). Tail flicks were counted at 5-min intervals for 35 min, starting 5 min after the injection of LEK-8804. Values are expressed as means ± SE of eight rats in each group.

onists, are unable to induce spontaneous tail flicks (33). That tail flicks induced by LEK-8804 are 5-HT_{1A} receptor mediated is in addition confirmed by the blockade of the response by the selective 5-HT_{1A} receptor antagonist NAN-190 at the dose of 0.16 mg/kg. At this dose, NAN-190 was previously found (33) to prevent the induction of spontaneous tail flicks by the selective 5-HT_{1A} agonist 8-OH-DPAT at the dose of 0.63 mg/kg. NAN-190 is selective within 5-HT receptors, but it is not selective with regard to α_1-adrenoceptors (13). However, as already mentioned above, α_1-adrenoceptors are not involved in the induction of spontaneous tail flicks.

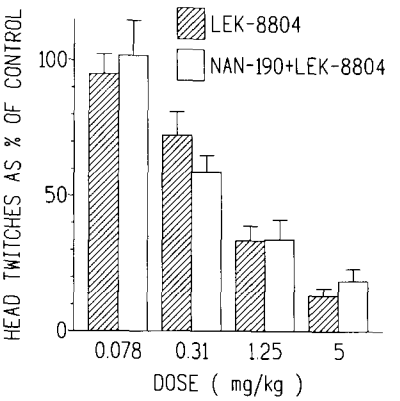

FIG. 4. Dose-dependent inhibitory effect of LEK-8804 on head twitch frequency in mice induced by 5-HTP/carbidopa (hatched bars), and failure of NAN-190 to modify this inhibition (clear bars). LEK-8804 was given IP at the doses shown either alone or mixed with NAN-190 (0.16 mg/kg), simultaneously with carbidopa (9 mg/kg, SC). 5-HTP (300 mg/kg, IP) was given after 15 min and the head twitches counted over a 5-min period after a further 30 min. Bars show means ± SE for nine mice expressed as percentages of paired vehicle-treated controls. Two-way ANOVA reveals a significant dose-dependent inhibitory effect of LEK-8804, $F(3, 64) = 47.77$, $p < 0.01$; the influence of NAN-190 upon the inhibitory effect of LEK-8804 is not significant, $F(1, 64) = 0.002$, $p > 0.05$.

Administration of LEK-8804 to mice dose-dependently inhibited the head twitch response induced by 5-HTP, the precursor of 5-HT. The head twitch-inducing effect of 5-HTP is considered to be a 5-HT_2 receptor-mediated response (8,18, 43). However, many other drugs in addition to 5-HT_2 antagonists are known to inhibit head twitches induced by 5-HT_2 receptor agonists (22). The inhibitory activities of α_2-adrenoceptor agonists (20,23) and 5-HT_{1A} receptor agonists (11) are probably most well characterised. Some ergoline derivatives were found to have very high affinity for α_2-adrenoceptors (35). According to preliminary unpublished data obtained from Panlabs service (Bothell, WA), the affinity of LEK-8804 for α_2-adrenoceptors is much lower in comparison with the affinity for 5-HT_{1A} and 5-HT_2 receptors. Therefore, α_2-adrenoceptors are less likely to be involved in the inhibitory effect of LEK-8804. To clarify the involvement of 5-HT_{1A} receptors in the inhibitory effect of LEK-8804 upon 5-HTP-induced head twitch response, in the present study the selective 5-HT_{1A} antagonist NAN-190 was injected concomitantly with LEK-8804. At the dose used (0.16 mg/kg), NAN-190 was not found to influence the 5-HTP-induced head twitches by itself; at this dose, in contrast, it prevented the occurrence of tail flicks in rats induced by LEK-8804. Thus, if the agonistic action of LEK-8804 on 5-HT_{1A} receptors were involved in its inhibitory effect upon 5-HTP-induced head twitches, NAN-190 would be expected to attenuate the inhibitory effect of LEK-8804. In the present study, however, this was not the case. Thus, the possibility that LEK-8804 antagonises the 5-HTP-induced head twitches by 5-HT_2 receptor antagonism is supported by exclusion of other possible mechanisms.

The simultaneous 5-HT_{1A} receptor agonistic and 5-HT_2 receptor antagonistic properties of a given compound might be promising in alleviating symptoms in certain psychiatric disorders. The brain 5-HT_{1A} as well as 5-HT_2 receptors are supposed to be important targets for alleviation of symptoms of anxiety and depression. The involvement of 5-HT_{1A} receptors in certain forms of anxiety and depression is supported by reports of the effects of selective 5-HT_{1A} agonists in both animal models (28,40) and human patients (1,15). Although clinically effective selective 5-HT_{1A} receptor agents such as buspirone, ipsapirone, and gepirone probably exert their effects via full agonist action on somatodendritic 5-HT_{1A} autoreceptors in the raphe nuclei and partial agonist action at postsynaptic 5-HT_{1A} receptors in the hippocampus (4,6), there is preclinical evidence that full postsynaptic 5-HT_{1A} agonists such as 8-OH-DPAT may also be effective (19,28). In addition to selective 5-HT_{1A} agonists, selective 5-$HT_{2/1C}$ antagonists have also been proposed to have anxiolytic and antidepressive properties in animal models (27,41) and certain forms of anxiety and depression in humans (6,10). As proposed by Glennon et al. (11), with regard to drug development the modulation of one 5-HT-mediated effect by a second 5-HT mechanism leading to the same specific effect may be a better approach than targeting research solely toward the development of receptor-selective agents. Considering the pharmacological profile of LEK-8804, one can speculate that this compound, acting as the 5-HT_{1A} receptor agonist and as a drug which (directly or indirectly) decreases the effects of 5-HT at the 5-HT_2 receptor level, might be a promising candidate for the treatment of anxiety and depression.

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