GENETICS

Effect of Antagonists and Agonists of 5-HT_1 and 5-HT_2 Serotonin Receptors on the Predator Aggressiveness of Wild Norway Rats

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The effect of agonists of serotonin receptors on predator aggressiveness (the "mouse killing" test) is studied on Norway rats. Ipsapirone and eltoprazine are found to have no effect on predator aggressiveness. 1-[3-(Trifluoromethyl)phenyl]piperazine×HCl (TFMPP) considerably reduces aggressiveness. The serotonin precursor 5-hydroxyptryptophan also lowers it, while the antagonist of 5-HT_{2A} receptors ketanserin abolishes the inhibitory effect of 5-hydroxytryptophan. Presumably, the inhibitory effects of serotonin on predator aggressiveness are realized via the 5-HT_{2A} and 5-HT_{2C} brain serotonin receptors.

Key Words: *predator aggressiveness; types of serotonin receptors*

More than 15 types and subtypes of serotonin receptors have been identified, cloned, and sequenced. Three types of brain serotonin receptors, namely 5-HT_1 and 5-HT_2 receptors, coupled to the G-protein superfamily, and 5-HT_3 receptors, an ion channel component, have been extensively studied. 5-HT_1 and 5-HT_2 receptors are encoded by structurally different genes, are coupled to different second messengers (adenylate cyclase and phospholipase C, respectively), and differ in their distribution in brain structures and sensitivity to agonists and antagonists of serotonin receptors [6,9]. At least five subtypes of 5-HT_1 serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}) and three types of 5-HT_2 (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}) have been identified [9]. Obviously, the role of serotonin in the regulation of serotonin-dependent types of behavior cannot be elucidated without a knowledge of the characteristics of these serotonin receptor types. Meanwhile, information regarding the participation of various 5-HT receptors in the regulation of behavior is scarce. This also applies to predator aggressiveness, a type of behavior which is widespread in nature and manifests itself as specific, nonaffective aggressiveness associated with feeding behavior but to a certain degree independent of it [2]. Predator aggressiveness has been studied predominantly on laboratory rats which kill mice; however, this type of behavior is most pronounced in wild rats [10]. There is considerable evidence that serotonin inhibits predator aggressiveness in various animal species [2,3].

The aim of this study was to evaluate the involvement of the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C} types of serotonin receptors in the regulation of predator aggressiveness in wild Norway rats.

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MATERIALS AND METHODS

Experiments were performed on 5-month-old male Norway rats (*Rattus norvegicus*) weighing 220-370 g. The animals were maintained under standard vivarium conditions and natural light. Two or three days prior to experiments they were placed in individual cages (50×33×20 cm) to eliminate the group effect. The rats had free access to food and water.

Predator aggressiveness was evaluated in the mouse killing test. An outbred albino mouse weighing about 20 g was placed in a rat's cage for 40 min. The rat killed it by biting it in the neck, after which the mouse was removed from the cage to prevent its being eaten. The number of rats killing mice was recorded in each group.

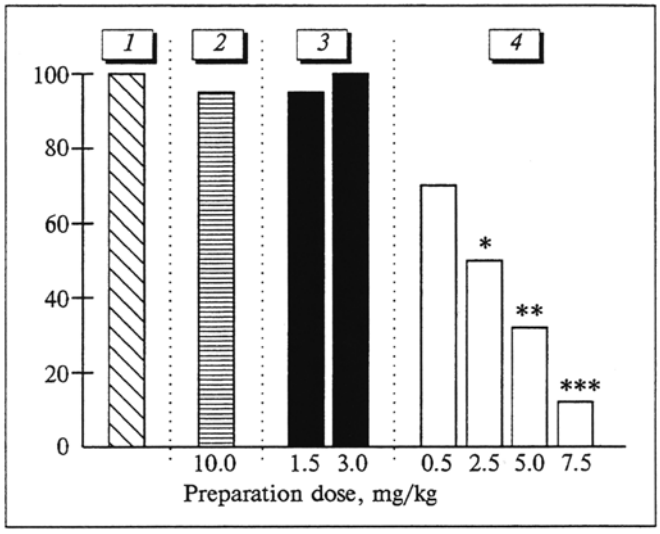

Fig. 1. Effects of physiological control (*1*) and of the agonists of 5−HT_{1A} serotonin receptors ipsapirone (*2*), of 5−$HT_{1A/1B}$ receptors eltoprazine (*3*), and of 5−$HT_{1B/2C}$ receptors TFMPP (*4*) on the predator aggressiveness of Norway rats. Here and in Fig. 2: the ordinate gives the percentage of rats killing mice; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ compared with the control.

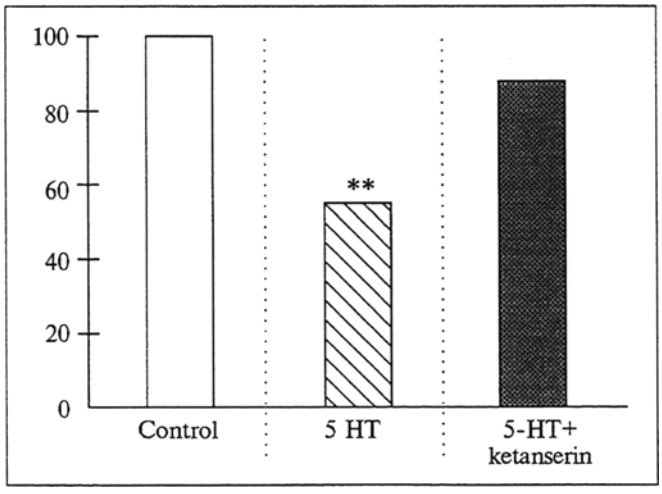

Fig. 2. Effect of the antagonist of 5−HT_{2A} serotonin receptors ketanserin (2.5 mg/kg) on the inhibition of predator aggression by 5−hydroxytryptophan (5−HT, 100 mg/kg).

The following preparations were used: the agonist of 5-HT_{1A} receptors ipsapirone (Tropenwerke, 10 mg/kg), the agonist of 5-$HT_{1A/1B}$ receptors eltoprazine (1-[2,3-dihydro-1,4-benzodioxane-5-il]-piperazine×HCl (Dufar, 1.5 and 3 mg/kg), the agonist of 5-$HT_{1B/2C}$ receptors 1-[3-(trifluoromethyl) phenyl]piperazine×HCl (TFMMP, Dufar, 0.5, 2.5, 5, and 7.5 mg/kg), the antagonist of 5-HT_{2A} receptors ketanserin (Sigma, 2.5 mg/kg), and 5-hydroxy-D,L-tryptophan (Sigma, 100 mg/kg). All preparations were injected intraperitoneally. Control animals were injected equal volumes of normal saline. The tests were performed 30 min after the administration of preparation or normal saline. Each group consisted of at least 10 rats.

The results were analyzed using Pierson's χ^2 test and Student's t test.

RESULTS

Administration of the specific 5-HT_{1A} receptor agonist ipsapirone and the mixed 5-$HT_{1A/1B}$ agonist had no effect on predator aggressiveness in wild rats (Fig. 1). Thus, it can be concluded that the 5-HT_{1A} and 5-HT_{1B} receptors do not play any significant role in the regulation of this type of behavior.

On the other hand, the 5-$HT_{1B/2C}$ receptor agonist TFMPP elicited a distinct dose-dependent effect on predator aggressiveness: the number of rats killing mice dropped 2-fold after its administration in a dose of 2.5 mg/kg ($p<0.05$) and 10-fold after administration in a dose of 7.5 mg/kg ($p<0.001$, Fig. 1). Since the mixed agonist of 5-$HT_{1A/1B}$ receptors eltoprazine had no effect on this type of behavior and the 5-$HT_{1B/2C}$ receptor agonist TFMPP elicited a pronounced inhibitory effect, it can be assumed that the inhibitory effect of TFMPP is associated with activation of the 5-HT_{2C} receptors. This assumption is corroborated by evidence that the sensitivity of 5-HT_{2C} receptors to TFMPP is 10 times as high as that of 5-HT_{1B} receptors [8].

Changes in predator aggressiveness were observed after subtype A 5-HT_2 receptors were tapped. Administration of 5-hydroxytryptophan, a precursor of serotonin, resulted in pronounced inhibition of predator aggressiveness ($p<0.01$), which agrees with published data [2]. The specific antagonist of 5-HT_{2A} receptors (previously referred to as 5-HT_2 receptors) ketanserin (2.5 mg/kg) abolished the inhibitory effect of 5-hydroxytryptophan (Fig. 2).

Thus, we did not detect any effect of 5-HT_{1A} and 5-HT_{1B} serotonin receptors on the predator aggressiveness of wild Norway rats. These findings

suggest that the inhibitory effect of serotonin is realized via the 5-HT_{2A} and 5-HT_{2C} receptors.

5-HT_{2C} receptors, until recently wrongly considered to be 5-HT_{1C} receptors, are now referred to as type 2 serotonin receptors [9], since 5-HT_{2A} and 5-HT_{2C} are highly homologous in amino acid sequence, the intron/exon characteristics of their genes are similar, and they have the same second messenger system (stimulation of phospholipase C) and similar sensitivity to a number of selective ligands. It is noteworthy that 5-HT_{2C} and M-cholinoreceptors utilize the same chlorine channels [7]. Since acetylcholine is a major inducer of predator aggressiveness [2], the competition for ion channels that results in a diminution of cholinergic influences may be one of the mechanisms responsible for the inhibition of predator aggressiveness after the activation of type 2 serotonin receptors.

Our results indicate that not only different neurochemical mechanisms [2] but also different types of receptors of the same neurotransmitter system are involved in the regulation of different types of aggressive behavior. This applies above all to the 5-HT_{1A} serotonin receptors. Neither ipsapirone, a specific agonist of 5-HT_{1A} receptors, nor eltoprazine, an agonist of 5-$HT_{1A/1B}$ receptors, had any effect on predator aggression in rats. However, the 5-HT_{1A} receptors evidently do play an important role in the regulation of affective types of aggressive behavior [1,5]. In a dose of 10 mg/kg ipsapirone had no effect on "cold" predator aggressiveness but had a pronounced inhibitory effect on aggressive behavior with a strong emotional component: aggression induced by electric shock and by fear of a human being [1]. It is obvious that although serotonin is involved in the control of some types of aggressive behavior as an inhibitory neurotransmitter, different types of receptors participate in the regulation of different types of aggressiveness. This makes it possible to independently manipulate the expression of individual types of aggressive behavior and helps in the search for selective pharmacological control over various types of aggressiveness.

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