# From genes to aggressive behavior: the role of serotonergic system

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**Summary**
**Recent investigations in neurogenomics have opened up new lines of research into a crucial genetic problem—the pathway from genes to behavior. This paper concentrates on the involvement of protein elements in the brain neurotransmitter serotonin (5-HT) system in the genetic control of aggressive behavior. Specifically, it describes: (1) the effect of the knockout of MAO A, the principal enzyme in 5-HT degradation, (2) the association of intermale aggression with the polymorphism in the *Tph2* gene encoding the key enzyme in 5-HT synthesis in the brain, tryptophan hydroxylase (TPH), and (3) the effect of selective breeding for nonaggressive behavior on 5-HT metabolism, TPH activity and 5-HT$_{1A}$ receptors in the brain. The review provides converging lines of evidence that: (1) brain 5-HT contributes to a critical mechanism underlying genetically defined individual differences in aggressiveness, and (2) genes encoding pivotal enzymes in 5-HT metabolism (TPH and MAO A), 5-HT-transporter, 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors belong to a group of genes that modulate aggressive behavior.**
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## Aggressive behavior: evolutionary considerations of biological and social role

Aggressive behavior plays a significant role in the fitness of animals, and it is widespread in the animal kingdom. Animals use aggression to defend themselves and their progeny from attack by predators, to fight for females, to feed, and to maintain the social hierarchy. The study of aggressiveness is complicated, however, by the fact that aggressive behavior is not a unitary trait. The first and most influential classification related to preclinical aggression was proposed by Moyer.[1] The classification was based on the eliciting stimuli and included the following types of aggression: predatory (attacks on prey), intermale, fear-induced, irritable, territorial, maternal and instrumental aggression.

Although most of the research on the genetics of aggression has been done with mice, much of the scientific and public interest is sparked by concern about the role of heredity in human aggression.[2] One of the main reasons is the apparent increase in levels of aggression in human society. According to a World Health Organization Report,[3] violence is a major public health problem worldwide. It has to be noted that the number of victims of interpersonal violence (almost one person every minute) is almost twice as high as the number of people killed in armed conflicts. Although it is widely recognized that it is difficult to define the different types of aggression in humans, it is evident that offense and defense, infanticide and even, in some situations, predation do occur in humans.[2,4] A genetic contribution has been found for nearly all behavioral disorders that have been investigated in humans, including panic disorder and antisocial personality disorder.[5,6] Understanding the mechanisms responsible for a predisposition to aggression and violence is therefore an important goal in modern neurogenomics. At the same time, a lot of data demonstrate the validity of animal models for the study in behavioral genetics. The various Genome Projects revealed very high homology of human, mouse and rat genes as well as syntenic similarities. The Rat Genome Sequencing Project Consortium showed that rat, mouse and human genomes encode similar numbers of genes and suggested that 86–94% rat genes have orthologous genes in the mouse and 89–90% in the human.[7] Although the mouse became the dominant model for geneticists, the rat has been the favorite model for behavior physiology.

Another interesting aspect of aggressive behavior is the evolutionary role played by this kind of behavior in the domestication of animals. Domestication is one of the greatest achievements of man as well as the greatest biological experiment. The first chapter of Charles Darwin *The Origin of the Species* was devoted to the transformation of wild animals into domesticated species, serving as an example of

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Abbreviations: 5-HT, serotonin; TPH, tryptophan hydroxylase; MAO, monoamine oxidase; 5-HIAA, 5-hydroxyindoleacetic acid; SERT, serotonin transporter.

artificial selection motivated by the practical needs of man. Animals were first domesticated in ancient time, with most of the species in the Stone Age. Although the history of domestication of animals does not go back more than 15 thousand years, domestic animals differ from their wild ancestors much more than do even some genera. At the same time, different species of domestic animals exhibit a homologous variability with respect to many phenotypic features, and the main criterion and the common feature of all domestic animals is their ability to have direct contact with man and not to be afraid. This means that fear-induced aggression has been reduced in domestic animals.[8] Dmitry Belyaev[9] proposed that selection for behavior was carried out in the earliest stages of animal domestication with the tamer animals being retained for breeding and the more difficult or even impossible to handle aggressive animals being discarded.

To test this hypothesis, a unique experiment on the domestication of silver foxes was started almost 50 years ago.[9] The main aim of the experiment was, by means of selection for tame behavior, to obtain animals similar in their behavior to the domestic dog, so the main selection criterion was the reaction of foxes to human contact. The selective breeding for the lack of aggressive response to man was quite effective.[10] In contrast to wild-type animals, the foxes of the selected population are not afraid of people, and display, like dogs, an active positive reaction to human contacts (Fig. 1). Similar selective breeding for high and low aggressiveness was also performed on another species, Norway rat.[11,12] These experiments, firstly, developed the experimental models to study the process of domestication, and, secondly, demonstrated a significant role of the genotype in aggressive behavior.

**Figure 1.** Silver foxes selectively bred for many generations for nonaggressive behavior and displaying positive reaction to human contact.

However important the elucidation of the contribution of genetic factors to aggressive behavior might be, this approach does not give an answer to the principal questions: which candidate genes might be responsible for differences between highly aggressive and nonaggressive animals, and in what way can gene activity change behavior and make an animal or a man more or less aggressive?

## Brain neurotransmitters as key players in behavior regulations: brain 5-HT and aggressive behavior

It has long been clear that there are no genes controlling behavior directly, but that there are behavior regulators in the brain. Numerous neurophysiological, neurochemical and neuropharmacological studies demonstrated a pivotal role of brain neurotransmitters in the regulation of emotionality and behavior while current knowledge indicates that behavior-affecting genes might act via brain neurotransmitters.

The problem of searching for the genetic and neurochemical determinants of aggressive behavior is complicated by their apparent heterogeneity. In fact, aggressive behavior is complex trait, regulated by multiple genetic factors as well as by a set of neurotransmitters. At least 16 genes have been reported to affect some aspects of offense.[2] At the same time, it is evident that, for effective regulation, the number of genes and neurotransmitters must be limited and, therefore, the contribution of different candidate genes must be different; some genes and neurotransmitters must predominate for most kinds of behavior. This idea is in accordance with the numerous neurophysiological and neurochemical data, as well as with the data of QTLs. Brodkin et al.[13] identified QTLs that contribute to individual mouse strain differences in intermale aggression and mapped two loci on distal chromosome 10 and proximal chromosome X.

Brain neurotransmitter 5-HT functioning is implicated in the regulation of aggressive behavior and is of interest for several reasons:

1. It is evolutionarily very ancient
2. The early expression of 5-HT during prenatal development and its widespread effects on brain morphogenesis has led to the hypothesis that 5-HT plays a critical role in the brain development.[14,15]
3. Pharmacological data implicate 5-HT-ergic processes in the regulation of aggressive behavior in the crayfish,[16] fish,[17] birds,[18] mammals,[19–21] and humans.[22,23]
4. A vast body of pharmacological and neurochemical evidence implicate brain 5-HT in the regulation of different kinds of aggressive behavior in rats and mice;[24–26]
5. Clinical evidence associates impulsivity, aggression and suicide attempts, which are considered as aggression directed against the self,[27] with deficiency in central 5-HT activity.[23,28]

### Arguments for enzymes of 5-HT metabolism and 5-HT receptors as protein determinants in genetic control of aggressive behavior

5-HT and the other "classical" neurotransmitters (norepinephrine, dopamine, acetylcholine, GABA) are not proteins. However, in accordance with the central genetic dogma, DNA–RNA–protein, proteins must be involved in the effect of genes on the 5-HT system, presumably through the regulation of its synthesis, uptake and degradation.

The functioning of the 5-HT system in the brain depends upon three different mechanisms: (i) 5-HT synthesis and degradation, (ii) 5-HT reuptake from synaptic cleft, and (iii) the density and sensitivity of 5-HT receptors. Therefore, the candidate genes may encode pivotal enzymes in 5-HT metabolism, the 5-HT transporter (SERT) and 5-HT receptors.

Brain 5-HT is synthesized in a two-step reaction from amino acid tryptophan (Fig. 2). Two enzymes catalyze serotonin synthesis—tryptophan hydroxylase (TPH) and decarboxylase of aromatic *l*-amino acids. The principal enzymes in serotonin degradation are monoamine oxidase A and B (MAO A, MAO B). TPH carries out the first step and is the rate-limiting enzyme in 5-HT biosynthesis. Moreover, it is the only really specific enzyme in 5-HT metabolism. In contrast, the decarboxylase of *l*-aromatic amino acids is a widespread nonspecific enzyme. The non-specific character of this enzyme allows us to exclude it from the list of potential key players in the gene—5-HT system—aggressive behavior pathway, thus leaving TPH, MAO and SERT. So, the scheme of genetic regulation of aggressive behavior may be presented like this:

*gene—protein (TPH, MAO, 5-HT transporter)—changes in 5-HT metabolism and 5-HT neurotransmission—changes in functional state of brain 5-HT system—changes in 5-HT-regulated aggressive behavior*

There are other protein elements in neurotransmitter systems—receptors, and the gene–behavior pathway via 5-HT receptors is shorter than the model involving metabolic enzymes, i.e. *gene—protein (5-HT receptor)—serotonin-dependent behavior.* This review summarizes data showing that one of the critical mechanisms underlying genetically defined aggressiveness involves protein elements of the brain 5-HT system.

#### *Involvement of TPH in various genetic models of aggressive behavior*

The enzyme TPH belongs to a small family of structurally and functionally related aromatic acid hydroxylases that utilizes tetrahydropterins as substrates. In eukaryotes, these enzymes are composed of a homologous catalytic domain to which highly conserved C-terminal tetramerization regions and length- and sequence-specific N-terminal regulatory domains are attached.[29] About 15 years ago, the first TPH gene in rat,[30] mouse[31] and human[32] was described and, for most of this time, this gene has been thought to be the only TPH gene in the genome. Later, evidence accumulated indicating different biochemical properties in TPH enzymes depending on the analyzed tissue. However, efforts undertaken to identify TPH gene isoforms were unsuccessful till Diego Walther with colleagues generated knockout mice that were genetically deficient for TPH.[33] These mice lacked 5-HT in the blood, in the periphery tissues and in the pineal gland. However, there was only a minor 5-HT decrease in the brain structures. These surprising results, suggesting the existence of another gene not affected by the gene targeting, led Diego Walther and colleagues to the discovery of a second TPH gene in the genome of mice, rats and humans, called *Tph2*. It has been shown that *Tph2* is predominantly expressed in the brainstem and located on human chromosome 12 and mouse chromosome 10.[33,34] TPH1 and TPH2 enzymes are highly homologous proteins exhibiting 71% of amino acid identity in humans; however, the N-terminals containing the regulatory domain are quite different.[34]

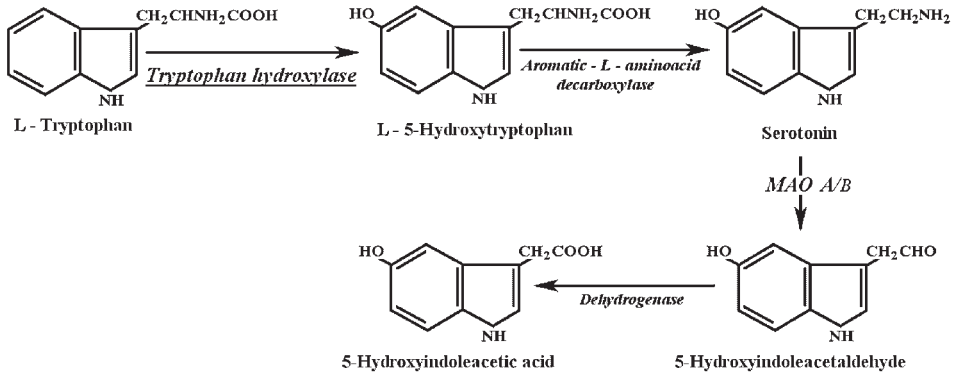


**Figure 2.** Serotonin metabolism in the brain.

This is new and important information, which contradicts previous ideas on the TPH gene. It proves that there are two 5-HT systems with independent regulation and distinct functions defined by two *Tph* genes: *Tph1* is expressed in the periphery and the pineal gland. *Tph2*, in contrast, is expressed in the brain and is responsible for the central nervous system effects of 5-HT. It is interesting to note that 20 years ago, while studying brain and peripheral 5-HT effects on thermoregulation, we suggested that ''along with the brain 5-HT mechanism there exists a peripheral 5-HT-ergic mechanism different from the central one''.[35] The finding of *Tph1* and *Tph2* genes has confirmed this hypothesis.

In 2004, the C1473G single-nucleotide polymorphism in the *Tph2* gene, which results in the replacement of $Pro^{447}$ by $Arg^{447}$, was demonstrated by Zhang with colleagues.[36] These authors also showed that this polymorphism might be important in 5-HT synthesis in the brain. It was found that mice of 129X1/SvJ strain homozygous for the 1473C allele (C/C) had higher 5-HT levels and an elevated rate of in vivo conversion of tryptophan to the 5-HT precursor, 5-hydroxytryptophan, in the frontal cortex and striatum, compared to mice of BALB/cJ strain homozygous for the 1473G allele (G/G).[36] Last year, we confirmed C1473G polymorphism in ten inbred mouse strains and provided strong evidence of a close link of *Tph2* alleles to enzyme activity and aggressive behavior.[37] TPH activity in the midbrain of mice homozygous for the 1473C allele was significantly higher than in mice carrying 1473G alleles. Importantly, it was found that substitution of C/C by G/G alleles was associated with a considerable decrease in the intensity of intermale aggression. It was shown that mice of C/C genotype attacked an intruder mouse more frequently than mice of G/G genotype. These results indicate a close association between *Tph2* gene alleles, brain TPH activity and aggressiveness in mouse strains. It is interesting to note that the more aggressive C/C genotype was prevalent: among 10 genotyped inbred mouse strains, C/C alleles were revealed in 7 strains and G/G alleles were found in 3 mouse strains.

At the same time, the replacement of C by G at the 1473 position of the *Tph2* gene does not influence another characteristic of intermale aggression—the penetrance of aggressiveness (the percentage of fighting mice).[37] Importantly, it had been shown earlier that the strain's penetrance, which reflects the threshold of the aggressive response—the ''hot temper'' of animals—did not correlate with the intensity of fighting. This suggests that these different patterns of aggressive behavior are controlled by different genetic mechanisms.[38] The data obtained presented additional confirmation of this idea.

Further evidence for *Tph2* involvement in genetic control of aggressive behavior came from experiments on selective breeding for nonaggressive behavior. It has been found that the selective breeding of Norway rats for the lack of aggression was followed by a marked change in brain 5-HT metabolism. Higher concentration of 5-HT and its main metabolite, 5-hydroxyindoleacetic acid (5-HIAA), and increased TPH activity was found in the midbrain of rats with genetically defined low aggressiveness compared with highly aggressive rats.[39] Similar changes in 5-HT metabolism were found in silver foxes selectively bred for more than 30 years for nonaggressive behavior to man.[20] Silver foxes displaying friendly responses to human contact were shown to have higher 5-HT and 5-HIAA levels, and higher TPH activity in the midbrain and hypothalamus in comparison to nonselected wild-type silver foxes bred in captivity. Importantly, the changes were found in the midbrain representing the area of main location of TPH2-synthesizing cell bodies. These findings were interpreted as an indication of an increased activity of the brain 5-HT system in the tame animals and, subsequently, a decreased activity of this system in highly aggressive animals. The remarkable consistency obtained in such diverse species as silver foxes and Norway rats suggests the involvement of the brain 5-HT system in the control of fear-induced defensive aggression in various species. It convincingly supports our hypothesis[21] that 5-HT system plays an essential role in brain mechanisms converting wild aggressive animal into tame counterparts, which is the background of domestication of animals.

The increased activity of TPH, which is considered as a marker of the 5-HT system's functional activity, and the increased 5-HT levels in the brains of nonaggressive rats and silver foxes are in good agreement with pharmacological data that implicates 5-HT as an inhibitory factor in fear-induced defensive aggression. In contrast, a positive association between TPH activity and intermale aggression in mice was shown.[37] The apparent discrepancy in the findings may be a matter of difference between species. However, although we may not completely understand the exact mechanism of 5-HT involvement in the regulation of aggression, we do know that *Tph2* may contribute to the expression of aggressive behavior.

### *MAO A and B genes: lessons from knockout mice*

MAO catalyzes oxidative deamination of monoaminergic neurotransmitters, 5-HT, noradrenaline and dopamine. There are two forms of MAO (A and B) that are involved in 5-HT metabolism. MAO A and MAO B enzymes are encoded by different genes[40] localized on the X-chromosome.[41,42] MAO A has a higher affinity to 5-HT than MAO B and is considered as the principal enzyme of 5-HT degradation.

Important clues into the roles of these isoforms come from the knockout studies. A line of transgenic mice has been generated in which the gene that encodes MAO A was disrupted.[43] Mice with the MAO A knockout (Tg8) differed from wild-type C3H mice by increased aggressiveness.[43,44] Tg8 mice have been found to lack brain MAO A activity and to have elevated 5-HT levels and lowered concentrations of the main 5-HT metabolite, 5-HIAA.[43,45] In MAO A-deficient mice,

there was a significant decrease in the 5-HIAA/5-HT ratio in the brain regions.[45] Despite the pronounced differences between various brain regions in this value, the relative 5-HIAA/5-HT ratio decrease in Tg8 mice versus the control C3H strain was surprisingly similar (to 45%) in all six brain structures studied. A lowered 5-HIAA level and 5-HIAA/5-HT ratio suggested a decreased functional activity of the 5-HT system in the brain of Tg8 mice. This suggestion is confirmed by electrophysiological data. It has been shown that the spontaneous firing frequency of 5-HT neurons was significantly reduced in MAO A knockout mice compared to wild-type controls.[46] In contrast, no changes in 5-HT level were found in the brain of MAO B-deficient mice, and MAO B knockout male mouse did not exhibit aggression.[47,48]

Very interestingly, the MAO A-deficient mouse strain provides a model for MAO deficiency in man. Indeed, some years ago, a Dutch family with a point mutation in the 8$^{th}$ exon of the structural MAO A gene was found by Brunner et al.[49] Four generations of this large kindred were examined, and 14 affected men with a complex behavioral syndrome characterized by borderline mental retardation and behavioral abnormalities with impulsive aggression were described.[50] In MAO A-deficient mice, changes in the level of catecholamines, 5-HT and their metabolites, as well as in aggressiveness[43,45] are similar to those found in the Dutch family.[49,50] It is interesting to note that the association of a regulatory polymorphism in the promoter region of the MAO A gene with antisocial alcoholism in 303 alcohol-dependent German descent male subjects including 59 alcoholics with antisocial personality disorder was described.[51]

Taken together, these results suggest that MAO A and MAO B play distinctly different roles in genetic control of aggressive behavior. Whereas MAO A is implicated in the genetically defined aggression in mouse and man, MAO B-deficiency affects neither 5-HT metabolism in the brain nor aggressive behavior.

### *Serotonin transporter gene*

Most of the 5-HT molecules released into the synaptic cleft are inactivated functionally by active transport of 5-HT from the extracellular space into 5-HT terminals. The reuptake mechanism allowing the same 5-HT molecule to be used repeatedly is mediated by plasma membrane 5-HT transporter (SERT), which is expressed selectively on 5-HT neurons. SERT terminates 5-HT action at the synapse and represents one of the key regulators of 5-HT-ergic activity providing effective control over the intensity 5-HT-mediated signaling.[52,53] Deletion of SERT in knockout mice produces a reduction in aggressive behavior: SERT-knockout males in resident-intruder test have longer latency before attacking the intruder and the number of attacks was decreased compared to control mice.[54]

### *5-HT receptor genes and aggressive behavior*

Another group of proteins that belong to the brain 5-HT system is the 5-HT receptor superfamily. In recent decades, 14 different subtypes of 5-HT receptors were described, which were subdivided in seven families based on operational (drug-related), transductional (receptor coupling), and structural (primary amino acid sequence) characteristics. All 5-HT receptors except one (5-$HT_3$ type) are metabotropic G-protein-coupled receptors; structurally and functionally distinct from all the other 5-HT receptor types, the 5-$HT_3$ receptor is an ionotropic ligand-gated ion-channel receptor.

Among an impressive variety of cloned and identified 5-HT receptors, particular attention has focused on the 5-$HT_{1A}$ receptor. This attention has been due to the available selective agonists and antagonists of the 5-$HT_{1A}$ receptor and the data on its involvement in the control of (i) anxiety and depression,[55–58] (ii) the autoregulation of 5-HT neurons in the brain[59] and (iii) pharmacological data suggesting that 5-$HT_{1A}$ receptor function is linked to aggression. An inhibitory effect of 5-$HT_{1A}$ receptor agonists on agonistic and social behavior in mice and rats was shown.[60–64]

Considerable differences in 5-$HT_{1A}$ receptors were found in Norway rats bred for high aggression and for lack of aggressive reactions to man.[65] 5-$HT_{1A}$ receptor density, the receptor mRNA expression in brain structures and functional correlates for 5-$HT_{1A}$ receptors identified as 5-$HT_{1A}$ agonist 8-OH-DPAT-induced hypothermia and lower lip retraction (LLR) were studied. A significant decrease in $B_{max}$ of specific receptor binding of [$^3$H]8-OH-DPAT in the frontal cortex, hypothalamus and amygdala as well as a reduction in 5-$HT_{1A}$ receptor mRNA expression in the midbrain of aggressive rats were found. 5-$HT_{1A}$ receptor agonist 8-OH-DPAT (0.5 mg/kg, i.p.) produced a distinct hypothermic reaction in nonaggressive rats and did not affect significantly the body temperature in aggressive rats. Similar differences were revealed in 8-OH-DPAT-induced LLR: LLR was much more strongly expressed in nonaggressive than in aggressive animals.

Hence, genetically defined low aggressiveness was shown to be associated both with increased expression of 5-$HT_{1A}$ receptor mRNA in the midbrain, their density in some brain regions and functional activity of 5-$HT_{1A}$ receptors, suggesting an important role of the 5-$HT_{1A}$ receptor in the aggressive behavior suppression. This suggestion is in good agreement with pharmacological studies demonstrating inhibitory effects of 5-$HT_{1A}$ receptor agonists on different models of aggressive behavior in mice and rats. Moreover, our data are consistent with the studies carried out in man:

- an inverse correlation between response to 5-$HT_{1A}$ receptor agonist ipsapirone and aggression in man was shown: the subjects with a blunted neuroendocrine response to ipsapirone challenge had significantly higher self-ratings of aggressivity/[66]. Furthermore, there was a

significant negative correlation found between binding potential of 5-$HT_{1A}$ receptors measured by positron emission tomography and lifetime aggression;[67] a correlation of reduced 5-$HT_{1A}$ receptor binding in temporal cortex with aggressive behavior in Alzheimer disease has been described by Lai et al.[68] These authors suggested that 5-$HT_{1A}$ receptor Bmax represented the best predictor for aggression.

The decreased sensitivity of 5-$HT_{1A}$ receptors and the decreased 5-$HT_{1A}$ receptor density in the limbic system of aggressive rats found in our experiments are to some extent in accordance with similar results obtained on displaying aggressive phenotype MAO A-knockout mice.[45]

Taken together, the evidence reviewed above suggests that 5-$HT_{1A}$ receptors in the limbic system of the brain may fulfill a significant role in the expression of aggressiveness, and inherited high or low aggressiveness may be determined, at least partly, by the expression and density of 5-$HT_{1A}$ receptors in the limbic system.

At the same time, 5-$HT_{1A}$ receptor knockout mice display anxiety-related behavior,[57] but there are no indications of increased aggression.[69] Among the possible explanations of this apparent discrepancy is the fact that the gene knockout technique is excellent for animal models of human hereditary disease but it may have some limitations for studying the role of the gene in the physiology or behaviour of adult animals. There are two reasons for this. (i) The genetic defect is present from the earliest stage of ontogeny, throughout the growth of the nervous system. Compensatory genes may take over the function of the mutated gene, during the course of development;[70] Therefore, at least some of the changes observed in adult mice with genetic knockout may be caused by disturbances of developmental processes and are not associated with the functional role of the given gene in adult organism. ((ii)The deficiency of the 5-$HT_{1A}$-receptor gene in knockout mice results in a complete elimination of functionally distinct 5-$HT_{1A}$ receptors. It is well known that 5-$HT_{1A}$ receptors are localized both presynaptically and postsynaptically, and according to their localization, they exert different effect on the functional state of the 5-HT system. The stimulation of presynaptic receptors inhibits this system, whereas stimulation of postsynaptic receptors produces effects typical of the functional activation of the 5-HT system. The greatest differences between aggressive and nonaggressive rats are found in the brain areas where postsynaptic 5-$HT_{1A}$ receptors are predominantly located, i.e. in the frontal cortex, hypothalamus and amygdala. In these structures, the density of 5-$HT_{1A}$ receptors was decreased in highly aggressive rats. Thus, it can be proposed that, in mutant mice lacking both types of 5-$HT_{1A}$ receptor, the deficiency of postsynaptic 5-$HT_{1A}$ receptors in the limbic system can be counteracted by the deficiency of presynaptic 5-$HT_{1A}$ receptors.

Enhanced aggressive behavior was revealed in 5-$HT_{1B}$ receptor knockout mice.[71,72] Mice lacking the 5-$HT_{1B}$ receptor attacked the intruder faster and more intensely than wild-type mice: the attack latency decreased, and number of attacks increased in 5-$HT_{1B}$ knockout mice. These findings are supported by preclinical studies showing the attenuating effect of 5-$HT_{1B}$ receptor agonists on aggression heightened by social instigation, frustration or alcohol.[73–76] Importantly, a linkage of aggressive and impulsive behavior due to alcoholism with the 5-$HT_{1B}$ receptor gene was revealed in two human populations—in Finnish alcoholic criminal offenders and in a large multigenerational family from an American Indian tribe.[77]

The data on other 5-HT receptors are rather scarce. A selective 5-$HT_7$-receptor agonist SB 269970 did not produce any significant changes in isolation-induced agonistic encounters between male mice, suggesting that 5-$HT_7$-receptor might not be involved in the modulation of aggression.[78] The results of pharmacological analysis implicate 5-$HT_3$ receptor in the regulation of aggressive behavior and alcohol-heightened aggression in mice,[79] and a cocaine-induced aggressive response in hamsters.[80] At the same time, no changes were found in alcohol-induced intermale aggression in $HT_3$-overexpressing mice (TG), and 5-$HT_3$ antagonist zacopride reduced aggression in both TG and wild-type mice.[79] It was shown that 5-$HT_{2A/2C}$ receptor agonist $\alpha$-methyl-5-hydroxytryptamine microinjected into the periaqueductus gray matter decreased maternal aggression in rats.[81] However, to date there is no evidence concerning the role of these receptors in genetic regulation of aggressive behavior.

## Conclusions

This paper has considered the importance of certain pivotal proteins in one neurotransmitter system in the pathway that leads from genes to behavior. Combined with molecular, biochemical and pharmacological approaches, the reviewed data have elucidated a framework of mechanisms from which the mutant genes aggressive behavior. Here, specifically, we have reviewed the recent work of several groups that shows that genes encoding key enzymes in 5-HT metabolism (TPH2 and MAO A), SERT, and at least two types of 5-HT receptors (5-$HT_{1A}$ and 5-$HT_{1B}$) are involved in the genetic determination of aggressive behavior (Fig. 1). Each of these elements is able to play a characteristic role in establishing the aggressiveness as a trait characteristic of an individual. A major biological function of these *gene–brain 5-HT system* pathways, is the suppression of aggressive behavior. However, although the favorite neurogeneticist's model, the mouse, and the human physiologist's model of choice, the rat, have 86-94% orthologous genes[82] apparent discrepancy exists in the findings on these animal models. Whereas experiments on rats are mostly consistent with the 5-HT-deficiency hypothesis of aggression, there is evidence

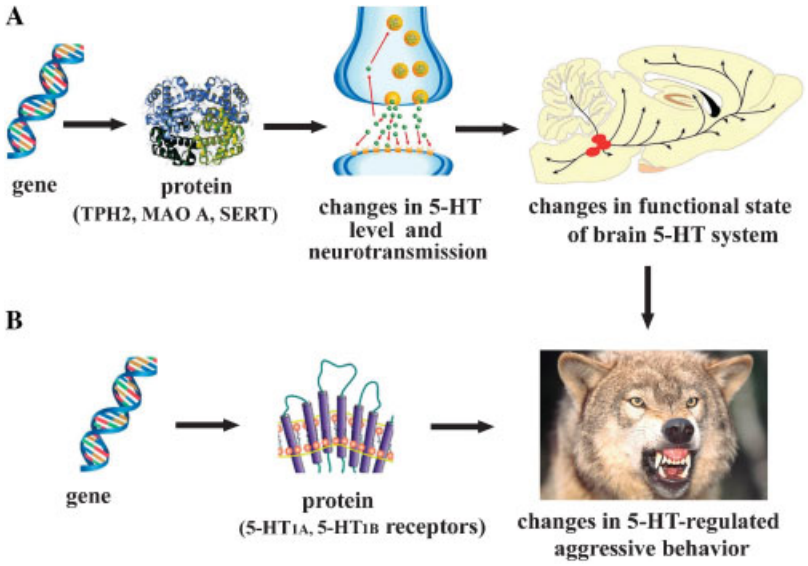


**Figure 3.** Schematic model of the pathway from gene to aggressive behavior via key enzymes in 5-HT synthesis (TPH2), degradation (MAO A) or transporter, SERT **(A),** and via shorter way involving 5-HT receptors **(B)**.

that a decrease in 5-HT biosynthesis attenuates the intensity of intermale aggression in mice.[37,83] We are, however, still at an early stage in the exploration of this fascinating area. Despite the advances in the understanding the role of 5-HT in genetic control of aggressive behavior, there are many questions that remain to be answered. Firstly, the exact mechanism by which the changes in brain 5-HT neurotransmission modulate aggressiveness remains to be elucidated. Secondly, while the changes in the 5-HT system during the aggressive act itself was not addressed in this review, it has to be mentioned that a display of defensive aggressive behavior is positively related to brief spikes of 5-HT neuronal activity.[84] Finally, although these results indicate the important role of the genes encoding pivotal proteins in 5-HT neurotransmission in modulation of aggressive behavior, the 5-HT system is certain to work in concert with other neurotransmitter genes. There is no doubt that a firing 5-HTergic neuron is connected with numerous other cells and receives impulses from different neurotransmitters. We can anticipate that functional studies of other individual genes will continue to provide insight into the genetic regulation of aggressive behavior. In conclusion, the substantial achievements made in our understanding of how genes may act on behavior, support the hope that diagnosis and genetic correction of abnormal aggressiveness may be within reach. Understanding the events behind hereditary aggressiveness will undoubtedly one day lead to new pharmaceuticals that help prevent the violence and aggression associated with these conditions (Fig. 3).

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