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Review

5-HT_{1B} receptors and aggression: A review

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Abstract

The serotonergic (5-HT) system in the brain is involved in the modulation of offensive aggressive behavior. The dogma that activity of the 5-HT system is inversely related to aggression is obsolete now. Research on the status of the 5-HT system before, during and after the execution of aggression is ongoing but has not yet led to a clear picture about the actual functional role of the 5-HT system, the more because state versus trait aggression seems to play a pivotal role in the outcome. Pharmacological challenges pinpoint 5-HT_{1A} and 5-HT_{1B} receptors as key players in the modulation of offensive aggression. This review emphasizes in particular the role of postsynaptic 5-HT_{1B} (hetero) receptors as a premier site to modulate offensive aggression. Modulation of the firing and 5-HT release of the serotonergic neuron, via presynaptic 5-HT_{1A} (auto) receptors, presynaptic 5-HT_{1B} (auto) receptors and serotonergic transporters, may also have striking influences on aggression under certain conditions. Therefore, it is hypothesized that postsynaptic 5-HT_{1B} (hetero) receptors directly influence the executive, consummatory phases of agonistic behavior, whereas presynaptic serotonergic feedback systems are particularly useful in the introductory (appetitive) phases of the agonistic behavioral complex.

Keywords: Serotonin; Aggression; 5-HT_{1B} receptor; 5-HT transporter; 5-HT_{1A} receptor

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1. Introduction to the serotonergic system, 5-HT receptors and 5-HT_{1B} receptors

The 5-HT system in the central nervous system contains a limited, but well-defined number of serotonergic cells. The cell bodies (soma) are mainly located in the mid-and hindbrain (Tork, 1990) and serotonergic neurons project both to rostral and caudal areas of the brain (Jacobs and Azmitzia, 1992). In

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particular, it is thought that the rostral projections play a big role in the involvement of the serotonergic system in the pathology of various psychiatric disorders.

The serotonergic system is complex and, in the last decades, an enormous volume of new findings has dramatically changed the simple concept of the neuron–neurotransmitter-receptor axis. At present, 14 different serotonin receptors can be distinguished within the serotonin receptor family: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, 5-ht_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-ht_{5A}, 5-ht_{5B}, 5-HT_6, and 5-HT_7. The 5-HT receptor family is part of two extended gene superfamilies; the G-protein coupled receptor superfamily and the ligand-gated ion channel superfamily. The 5-$HT_{1,2,4,5,6\ and\ 7}$ receptors are linked to the modulation of either adenylate cyclase or phosphoinositol turnover via G-proteins, whereas 5-HT_3 receptors modulate ion channels.

5-HT_{1A} receptors are localized presynaptically on the cell bodies and dendrites (so-called somatodendritically) of 5-HT neurons in the raphe nuclei and postsynaptically on many non-serotonergic neurons. 5-HT_{1B} (and 5-HT_{1D}) receptors are also localized pre- and postsynaptically; presynaptically, 5-HT_{1B} receptors are localized as so-called autoreceptors on serotonergic axon terminals (Zifa and Fillion, 1992), whilst postsynaptic 5-HT_{1B} receptors are heteroreceptors localized at axon terminals of non-serotonergic neurons (Boschert et al., 1994). All other 5-HT_{1B} receptors are presumably localized postsynaptically (Bonaventura et al., 1998).

A schematized 5-HT neuron is shown in Fig. 1; in addition to all 5-HT receptors, the 5-HT transporter is also represented. The 5-HT transporter is localized both at the terminal portion of the axon and at the cell body of the 5-HT neuron (Hoffman, 1993; D'Amato et al., 1987; Hrdina et al., 1990; Chen et al., 1992).

The activity of a serotonergic neuron is presumably regulated via two kinds of autoreceptor (5-$HT_{1A\ and\ 1B}$) and the 5-HT-transporter (Piñeyro and Blier, 1999) (Fig. 1). During neuron firing, serotonin is released from its terminals and activates for some time available 5-HT receptors. In order to regulate the firing and the release of serotonin, several feedback mechanisms are around to modulate the activity of the 5-HT neuron. First, 5-HT-transporters in the synaptic terminals, but also at the cell bodies and the dendrites of the 5-HT neurons bring 5-HT back into the neuron via an uptake mechanism. This process, 5-HT reuptake, is a very important mechanism of a cell to restore its resting condition in order to be able to fire again and to avoid overstimulation of receptors. A second mechanism contributing to ceasing cell firing and stopping release is activation of the 5-HT_{1B} autoreceptor at the level of the synaptic terminals, leading to a direct inhibition of 5-HT release. A third mechanism is constituted by the somatodendritic 5-HT_{1A} autoreceptors, which, upon activation, directly inhibit cell firing and, consequently, serotonin release. Whether the endogenous serotonin necessary for this inhibition derives from release of 5-HT from the somatodendritic areas themselves and/or originates from terminals from neighbouring cell in the raphe nuclei is not completely clear yet (Piñeyro and Blier, 1999; Adell et al., 2002). There is also evidence that 5-HT_{1B} receptors are present in the raphe nuclei, particularly in the median raphe nucleus (Adell et al., 2002), that upon activation are also involved in inhibition of the serotonergic neuron. The interplay of these various processes leads to an apparently highly fine-tuned system of firing patterns of serotonergic neurons, needed to modulate the various and extensive functions this neurotransmitter is involved in. However, it should be kept in mind that various other systems (e.g. GABA-ergic, noradrenergic, cholinergic, glutamatergic, dopaminergic and others (Adell et al., 2002; Piñeyro and Blier, 1999)) also influence serotonergic neurons and that the whole interplay of all contributing mechanisms determines the functional outcome of the activity of the serotonergic system.

The 5-HT_{1B} receptor, previously called 5-HT_{1B} in rodents and 5-$HT_{1D\beta}$ in other species including man, is now called r5-HT_{1B} and h5-HT_{1B}, respectively (Hartig et al., 1996). The

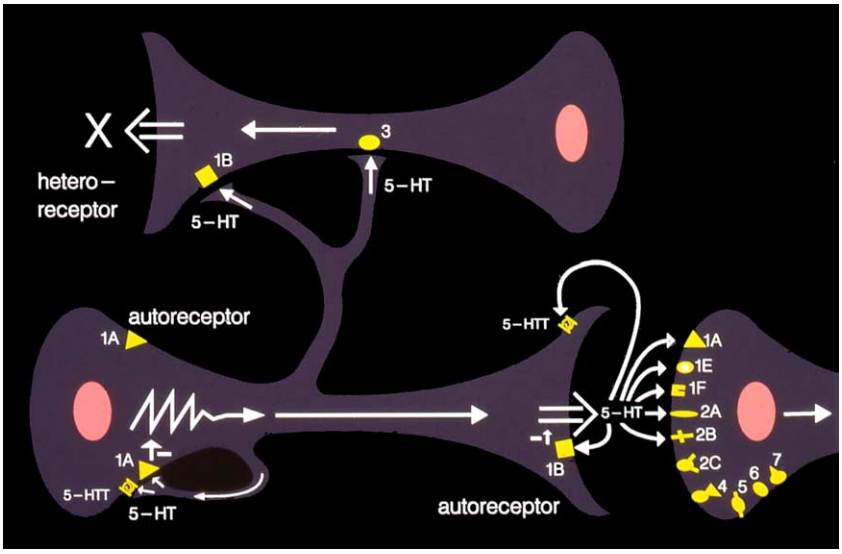

Fig. 1. A prototypic serotonergic neuron and the putative localization of the various serotonergic receptors and transporter on the 5-HT neuron and postsynaptic non-serotonergic neurons.

5-HT_{1B} receptors from different species have a large similarity and corresponding functions, but the pharmacology displayed by the rodent and non-rodent versions is quite different (Adham et al., 1992; Hamblin et al., 1992), although this difference is only due to a single amino acid difference (Asparagine versus Threonine) in the seventh transmembrane domain of the 7-TM receptor (Oksenberg et al., 1992; Metcalf et al., 1992). 5-HT_{1B} receptors have been found localized on serotonergic and non-serotonergic neurons, acting as presynaptic auto-and heteroreceptors, respectively, putatively regulating neurotransmitter release (Engel et al., 1986; Gothert et al., 1998; Maura and Raiteri, 1986). 5-HT_{1B} receptor mRNA is present in raphe nuclei, striatum, cerebellum, hippocampus, entorhinal and cingulated cortex, subthalamic nucleus and nucleus accumbens, but not in the substantia nigra or globus pallidus (Bonaventura et al., 1998; Bruinvels et al., 1994; Doucet et al., 1995; Jin et al., 1992; Maroteaux et al., 1992; Voigt et al., 1991). Autoradiographic visualization of 5-HT_{1B} receptors (protein) was found in partly different areas, including dense packing in ventral pallidum, globus pallidus, substantia nigra, dorsal subiculum and moderate dense packing in cerebral cortex, molecular layer of the hippocampus, entopeduncular nucleus, superficial gray layer of the superior colliculus, caudate putamen and deep nuclei of the cerebellum (Boulenguez et al., 1996; Bruinvels et al., 1993; Pazos and Palacios, 1985; Sari et al., 1999; Sari, 2004). This mismatch between synthesis and localization is explained by hypothesizing that this receptor is synthesized at a different place (cell body) and transported from there to axon terminals, both in serotonergic and non-serotonergic neurons (Boschert et al., 1994). No structural differences in 5-HT_{1B} autoreceptors and heteroreceptors have been reported, but some genetic variation in the h5-HT_{1B} receptors has been found (Gothert et al., 1998); a mutation in the third transmembrane domain has an allele frequency of 2% and bears a receptor with a deviant pharmacology from the wildtype (98% allele frequency). The functional consequences of these kind of genetic variations are unknown, but potentially could cause disturbances in CNS functioning.

In the present review, we postulate that postsynaptic 5-HT_{1B} receptors, present as heteroreceptors on terminals of non-serotonergic neurons (Sari et al., 1999; Sari, 2004), are critical in the modulation of (offensive) aggression. We have good evidence that this receptor is involved in the modulation of impulsivity and aggression.

First, a more general and historical picture is sketched of the emergence of the idea that 5-HT_{1B} receptors are important in the modulation of offensive aggression, the putative involvement of serotonin in aggressive behavior before turning to the specific role of 5-HT_{1B} receptors.

2. Aggression, serenics and 5-HT_{1B} receptor agonists

In the seventies of the last century, Solvay Pharmaceuticals (at that time Philips Duphar) started research in the area of aggression. The underlying idea was that there was a huge need for psychotropic drugs, specifically influencing aggression, without interfering with other important modalities. The drugs used clinically at those times (and still used now) were not at all specific for aggression but induced sedation, motor disturbances or other unwanted effects (Olivier and Mos, 1986; Olivier et al., 1986).

Based on a number of animal aggression paradigms, thousands of drugs were synthesized and tested on their anti-aggressive qualities (Olivier and Mos, 1986; Olivier et al., 1986; 1990a,b; 1994). At that time the screening for anti-aggressive properties of drugs was purely based on behavioral tests and only much later it became clear that in order to have specific anti-aggressive effects, drugs should have selective effects on certain 5-HT receptors. The primary screening test used was the isolation-induced aggression test in male mice (Olivier and van Dalen, 1982; Olivier et al., 1984). When male mice are isolated for a couple of weeks a percentage of them (usually around 50%) displays offensive aggression when they are confronted with a male conspecific. In this first screen only the number of attacks was counted during a short 3-min test and the potential anti-aggressive effects of a drug were only measured as a decrease in the attack frequency. After initial screening of hundreds of compounds, some interesting activities were found in a series of chemical compounds of the phenylpiperazine class (Olivier et al., 1986). Extensive structure-activity driven chemical synthesis led to potent compounds (potency <10 mg/kg PO in the isolation-induced aggression test). Because only specific anti-aggressive drugs were of interest, a number of animal aggression tests were developed, that were able to measure how specific the drugs inhibited aggressive behavior. These tests, mainly performed in rodents, were based on ethological observations of rodents in test environments engendering the possibility that animals could display their natural behavioral repertoire. In one of these tests, the resident–intruder paradigm in rats, male rats were housed either alone with a female, or as a pair of male rats with a female, in a large cage for several months. Under such conditions, the male (or one of the males of the pair) became the territorial or resident male in the cage; this could be easily seen when a strange male rat was introduced into the cage. After some exploratory behavior, the resident soon exhibited a whole array of agonistic activities towards the intruder, which, starting with initial defensive movements, soon surrendered showing submissive behaviors and producing ultrasonic (22 kHz) signals. Using ethological techniques, the frequencies, duration and sequence of occurrence of more than 30 behavioral elements were scored during short tests typically lasting 10 to 15 min (Olivier, 1981; Mos et al., 1992). These kinds of analyses provided detailed insight how drugs may influence behavior. In the case of the early anti-aggressive drugs (DU27725: *N*-[2-[4-[3-(trifluoromethyl)phenyl]-l-piperazinyl]ethyl] acetamide maleate (Olivier, 1981), DU28412 (Bradford et al., 1984), fluprazine (DU27716: [2-[4-[3- 8.9 (trifluoromethyl)phenyl]-1-piperaziny1]ethy1] urea hydrochloride) it was clear that these drugs affected offensive aggressive behavior in a very typical way. It appeared that only the consummatory aspects of aggression (the last behavioral elements in the sequence) were decreased, but that social activity was not affected. In contrast, social and overall

activity was even enhanced. This pattern induced by the anti-aggressive drugs was not found in any other drug from any other drug class tested so far (antipsychotics, benzodiazepines, alcohol, psychostimulants, antidepressants, anticholinergics, antihistaminergics, and anticonvulsants). Because the early anti-aggressive compounds, renamed SERENICS, appeared toxic at further testing in animals (teratogenic), further synthesis and testing of new drugs was performed in order to get rid of these toxicological effects whilst keeping the serenic effects. This operation appeared successful and led to the finding and development of eltoprazine (DU28853 (1-[2,3-dihydro-1,4-benzodioxin-y1]-piperazine), a highly potent and selective anti-aggressive drug (Olivier and Mos, 1986; Olivier et al., 1986).

In the mean time, receptorology started blossoming and showed that there were multiple serotonergic receptors, first showing 5-$HT_{1\ and\ 2}$ receptors, soon however followed by a further detection of subtypes of the 5-HT_1 receptor, viz. 5-$HT_{1A,\ 1B\ and\ 1C}$ receptors (the 5-HT_{1C} receptor was later renamed into the 5-HT_{2C} receptor). Testing of serenic compounds on these receptors revealed a high binding to 5-HT_{1A} and 5-HT_{1B} receptors. Extensive in vitro and in vivo studies into their molecular pharmacology confirmed that the drugs were (partial) agonists at the 5-HT_{1A} and 5-HT_{1B} receptors (Olivier et al., 1994).

The obvious question was whether the highly specific anti-aggressive effects of eltoprazine (and other related substituted phenyl piperazines) were due to activation of the 5-HT_{1A}, the 5-HT_{1B} or some interaction between both receptors. At that time, the second half of the eighties, neither selective 5-HT_{1B} receptor agonists, nor 5-$HT_{1A\ and\ 1B}$ receptor antagonists were available. However, highly selective 5-HT_{1A} receptor agonists were present (8-OH-DPAT (8-hydoxy-2-(*N*,*N*-di-*n*-propylamino)tetralin), flesinoxan). Testing these drugs in all the animal paradigms of aggressive behavior indicated that in some paradigms (resident–intruder tests in mice and rats, maternal aggression in rats), 5-HT_{1A} receptor agonists (buspirone, 8-OH-DPAT, flesinoxan) displayed anti-aggressive effects, although in a rather nonspecific way, inducing a lot of sedation or other unwanted side effects (Mos et al., 1992; Olivier et al., 1990a,b, 1994, 1989). However, in an animal aggression paradigm purely reflecting offensive aggression, hypothalamically induced attack behavior (Kruk et al., 1979; Lammers et al., 1988), 8-OH-DPAT and flesinoxan were not at all active, whereas serenics and some other drugs with 5-HT_{1B} receptor agonistic activity (like TFMPP (1-(3-trifluoromethylphenyl)piperazine) and mCPP (meta- chlorophenylpiperazine)), dose-dependently and specifically (locomotion was not affected) reduced attack behavior (Kruk, 1991; Van der Poel et al., 1982; Olivier et al., 1994, 1995). Moreover, TFMPP, which has relatively weak 5-HT_{1A} but strong 5-HT_{1B} and $_{2C}$-receptor agonistic activity, showed also a similar serenic profile as eltoprazine (Olivier and Young, 2002). The 5-HT_{2C} receptor as mediator of serenic activity could be excluded because eltoprazine, in contrast to TFMPP exerts 5-HT_{2C} receptor antagonistic activity (Olivier et al., 1994). The later discovery that eltoprazine also has 5-HT_3 receptor agonistic effect also was shown not to contribute to its serenic effects (Olivier et al., 1994).

Thus, there was quite convincing evidence that 5-HT_{1B} receptors were crucial for the highly selective anti-aggressive action of the serenics. However, because 5-HT_{1B} receptors are localized both pre- and postsynaptically it was of interest whether the serenic effects were caused by either of them. It was speculated that the activity serenic must be caused by postsynaptically localized receptors because activation of the presynaptic autoreceptor leads to inhibition of 5-HT release as does activation of 5-HT_{1A} autoreceptors by 5-HT_{1A} receptor agonists; both effects should then lead to comparable anti-aggressive effects, which clearly is not the case. In a first study to unravel the pre- versus post receptor mechanisms, male resident rats were injected locally into the raphe nuclei with the neurotoxin 5,7-DHT which destroys the serotonergic cells (Sijbesma et al., 1991), leaving postsynaptically localized 5-HT receptors unaffected (although changes in their number and affinity for serotonin may occur due to the lack of stimulation of these receptors by the absence of the endogenous ligand, serotonin). Although 5,7-DHT itself reduced aggressive behavior, eltoprazine still exerted its anti-aggressive effects in these animals, strongly suggesting that postsynaptic effects on 5-HT receptors (Sijbesma et al., 1991) caused eltoprazine's anti-aggressive effects. Further supporting evidence came from local intracerebral injection studies performed in residential male rats (Mos et al., 1992, 1993). Injection of eltoprazine in the brain third ventricle, aimed for activating postsynaptic 5-HT receptors, led to anti-aggressive effects, whereas injection of eltoprazine in the raphe nuclei (activating the somatodendritic 5- HT_{1A} autoreceptors) had no anti-aggressive effects. Injection of 8-OH-DPAT, a full 5-HT_{1A} receptor agonist into the raphe nuclei, however, also inhibited aggression, although in a highly nonspecific way. Although eltoprazine also exerts 5-HT_{1A} receptor agonistic activity its intrinsic activity at this receptor is apparently not high enough to induce a 8-OH-DPAT-like effect when injected directly into the raphe nuclei (Mos et al., 1993). All this evidence supported our theory that postsynaptic 5-HT_{1B} heteroreceptors mediate the specific anti-aggressive effects of eltoprazine and other serenics. Till so far no studies have been performed in which area(s) of the brain these 5-HT_{1B} receptors are located, although the basal ganglia seem a very likely candidate.

3. Is serotonin inhibitory in aggression?

The big dogma in the relationship between serotonin and aggression is that 5-HT inhibits aggression, mainly derived from studies in which serotonin levels in the brain were decreased by neurotoxic agents like *para*-chlorophenylalanine (pCPA) or 5,7- dihydroxytryptamine (5,7-DHT), that deplete serotonin from serotonergic cells. Such an inverse relationship between 5-HT and aggression, has been found in animals and humans, although in the latter measurements on 5-HT activity were based on CSF levels of the main metabolite of serotonin, 5-hydoxyindoleacetic acid (5-HIAA). Notwithstanding severe criticisms on this parameter, for many years it was the only measure in humans reflecting (indirectly) the functional status of the 5-HT system. In animals, 5-HT and 5-HIAA can be

measured directly in the brain and it could be assumed that the inverse relationship between functional serotonergic activity and aggression should easily be established. However, several contradictory results have been found and even reports of a positive relationship between 5-HT and aggression occur. In humans aggression is associated with suicidal behavior and both seem to be associated with low serotonergic function, although it is possible that both phenomena are independently regulated (see for an extensive discussion on the neurobiology of suicidal behavior: Mann, 2003).

Measurement of contents of 5-HT and 5-HIAA in postmortem brain tissue and determining a turnover rate from these two parameters was originally described to be lower in aggressive than in non-aggressive mice (Giacalone et al., 1968). Successively measuring CSF samples in humans more or less supported this serotonergic hypofunction (Brown et al., 1979; Kruesi et al., 1990; Linnoila et al., 1983). However, this 5-HT hypofunction or deficiency trait more recently has been associated with impulsivity and risk-taking behavior rather than aggression per se (Mann, 2003). A causal relation between 5-HT activity and aggression or impulsivity cannot be derived from static measurements of 5-HT or 5-HIAA measurements in brain tissue or CSF-fluid. A functional role of serotonergic neurons in the initiation, execution and stopping of aggression (Coccaro, 1989; Miczek et al., 2002) still has to be established although some progress have been made using in vivo microdialysis techniques in freely moving (aggressive) animals. This technique however, still lacks sufficient resolution because sample time (minutes) is still of a different magnitude than the actual behavior (seconds). Van Erp and Miczek (2000) measured extracellular serotonin (and dopamine) release in 10-min samples in the nucleus accumbens and prefrontal cortex in rats, before, during and after a 10-min aggressive interaction with a male conspecific. During the agonistic interaction no detectable change in 5-HT release was found in the nucleus accumbens, but 5-HT levels were already decreased during fighting in the prefrontal cortex. After the confrontation 5-HT levels in the prefrontal cortex remained lowered (compared to pre-confrontation baseline) for at least 1 h, whereas 5-HT in the nucleus accumbens was not affected. Dopamine levels were enhanced in both brain areas after (but not during) the agonistic confrontation. However, 5-HT levels were decreased in the nucleus accumbens of rats that have been conditioned to fight at a specific time each day over a 10-day period (Ferrari et al., 2003). In the latter experiments heart rate and dopamine release were concurrently measured and both were raised in anticipation of the fight. Apparently, the actual performance of aggression can be dissociated from the anticipation of a fight, where dopamine plays an important role in the physiological and behavioral sequels around the performance and anticipation of aggression, whereas serotonin seems to be particularly related to termination of aggression.

Measuring electrophysiological events happening in the serotonergic neurons during the performance of aggressive behavior would be very helpful in unraveling the precise role of the serotonergic system but this seems technically not yet feasible. Moreover, the serotonergic system is not made up of one homogeneous mass of cells but is electrophysiologically (Beck et al., 2004), anatomically and functionally differentiated. The dorsal and median raphe nuclei partly project to different areas of the forebrain and partly to the same areas (Kusjlic et al., 2003) and are the most prominent sources of serotonergic neurons innervating areas involved in the initiation, performance and termination of aggressive behavior. Interestingly, no systematic studies are performed thus far trying to delineate the role of the different serotonergic cell groups in various aspects of aggression, although local lesions or local application of drugs in the dorsal or median raphe nuclei have been performed. It is highly unlikely that all serotonergic cell groups are involved and selective blockade or activation of individual cell groups in determining its role in aggression would be very fruitful.

A recent approach to unraveling the role of the 5-HT system in aggression is studying the differences between highly aggressive and low-aggressive individuals as has recently been pursued by the group of Koolhaas (de Boer et al., 2003). They argued, based on the assumption that the individual level of aggression of a rat (offensive aggression) is part of an individual coping strategy of the animal and thus an important indicator of a trait-like behavioral and physiological response pattern. In their extensive studies on the endophenotypes of high-aggressive and non-aggressive rodents, serotonergic activity was also studied. In contrast to the existing theory of inversed relationship between 5-HT activity and aggression, a positive correlation was found between the level of trait-like aggression (high or low) and basal CSF concentrations of 5-HT and 5-HIAA (Van der Vegt et al., 2003). Moreover, levels of 5-HT and 5-HIAA after in vivo microdialysis in the frontal cortex did not differ between endophenotypes. Apparently, normal offensive aggression is positively related to serotonergic neuronal activity, whereas an inverse relationship probably exists between 5-HT activity and impulse-like violent aggression (Coccaro, 1989).

Thus a general pattern emerges where trait and state aggression are probably differentially regulated by the 5-HT system (and also other systems) although much more research is needed to substantiate this hypothesis.

3.1. 5-HT_{1B} receptors and aggression

The early serenics (fluprazine, DU28412, DU 27725, eltoprazine, batoprazine: Olivier et al. (1990a,b)) are mixed 5-$HT_{1A/1B}$ receptor agonist, leaving the 5-HT_{1A} receptor still as an option for mediating (part of) the anti-aggressive effect, but more recently synthesized 5-HT_{1B} receptor agonists including, e.g. anpirtoline, CP-94,253 (5-propoxy-3-(1,2,3,6- tetrahydro-4-pyridinyl)-1H-pyrrolo[3,2-b]pyridine) and zolmitriptan, are far more selective for this receptor and showed a similar, highly specific anti-aggressive effect, both in aggressive residential mice and in mice made more aggressive via low-doses of alcohol or social instigation (Fish et al., 1999; de Almeida et al., 2001; De Almeida and Miczek, 2002; Miczek and de Almeida, 2001). Preclinical studies of aggressive behavior using various 5-HT_{1A} receptor agonists, including the prototypic full agonist

8-hydoxy-2-(*N*,*N*-di-*n*-propylamino)tetralin (8-OH-DPAT), showed anti-aggressive effects in various species from invertebrates to primates and encompassed isolated as well as socially housed animals, males and females and laboratory and feral animals (for an overview: Miczek et al., 2002). Detailed ethological studies showed however, that these anti-aggressive doses coincide with effects on several non-aggressive elements of the behavioral repertoire compromising the specific anti-aggressive effect (Olivier et al., 1995). Recent studies (De Boer et al., 1999; Miczek et al., 1998a,b) confirm the non-specific anti-aggressive profile of 5-HT_{1A} receptor agonists like buspirone, ipsapirone and 8-OH-DPAT, in studies on rats and mice with excessive levels of aggressive behavior. However, certain 5-HT_{1A} receptor ligands, like alnespirone and S-l5535 (4-(benzodioxan-5-yl)l-(indan-2-yl) piperazine), display a different anti-aggressive profile when tested in male wild-type Groningen (WTG) rats, originally wild trapped and bred for many generations in the laboratory. These rats display a high spontaneous level of offensive aggression and spent in a 10-min resident–intruder test, from 25–50% of their time on attack behavior (De Boer et al., 1999, 2000). In their test (De Boer et al., 1999) eltoprazine showed a rather specific anti-aggressive profile, although some inactivity was found. WAY-100,635 (*N*-[2-[4-(2- methoxyphenyl)-1-piperazinyl] ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamine), a highly specific 5-HT_{1A} receptor antagonist, antagonized the anti-aggressive effects of all the 5-HT_{1A} receptor agonists but only partially that of eltoprazine clearly showing that the 5-HT_{1A} receptor plays a role in the modulation of aggressive behavior. A remarkable phenomenon was present here: alnespirone had an ED_{50} of approx. 1 mg/kg, buspirone approx. 0.5 mg/kg, 8-OH-DPAT approx. 0.007 mg/kg and eltoprazine approx. 0.3 mg/kg. If the affinity of the drugs for 5-HT_{1A} receptors is taken into consideration, a remarkable finding emerges: alnespirone (Ki=0.19 nM) and eltoprazine (Ki=40 nM) differ a factor 200 on this receptor. Although affinity cannot be directly translated in efficacy, it can be postulated that the potent anti-aggressive effect of eltoprazine in this aggressive WTG strain is largely due to its 5-HT_{1B} agonistic activity. However, alnespirone, but particularly S-15535 has an intriguing profile of specific anti-aggressive action. S-15535 is described as a highly selective 5-HT_{1A} receptor ligand exerting competitive antagonism at postsynaptic 5-HT_{1A} receptors and agonistic activity at presynaptic 5-HT_{1A} receptors (Millan et al., 1993, 1994, 1997), whereas alnespirone exerts agonistic effects on both pre- and postsynaptic receptors. S-15535 and alnespirone exerted a very specific anti-aggressive profile in the resident–intruder test on highly aggressive WTG rats (De Boer et al., 2000), with an anti-aggressive ED_{50} of approx. 0.5 mg/kg for S-15535 and 0.7 mg/kg for alnespirone. The behavioral profile induced by both ligands differed slightly however. Social exploration was not enhanced after S-15535 but strongly so after alnespirone, whereas social interaction was decreased after S-l5535 but not, or even enhanced after alnespirone (De Boer et al., 1999). Non-social exploration (exploration of the cage) was enhanced after S-15535 but not after alnespirone. Eltoprazine (Olivier et al., 1986) in resident–intruder paradigms clearly shows increases in social interactions and exploration next to the anti-aggressive effects, a profile slightly different from that of the pure 5-HT_{1A} receptor ligands. Again, the anti-aggressive and other effects of S-15535 and alnespirone could be completely blocked by the 5-HT_{1A} receptor antagonist WAY-100,635, showing that all effects were completely due to modulation at 5-HT_{1A} receptors. De Boer et al. (2000) suggest that the specific anti-aggressive effects were caused by activation of the somatodendritic 5-HT_{1A} autoreceptors. Activation of this receptor by acute treatment of agonists leads to shutting down of the 5-HT release of serotonergic neurons (Adell et al., 2002), thereby decreasing the activation of all other non-5-HT_{1A} receptors in the CNS (as far structures are innervated by serotonergic neurons descending from the dorsal and median raphe nuclei). As the behavioral output (aggression, social and non-social behavior and other behaviors) is influenced by the activity of (at least part of) the serotonergic system, a decrease in serotonin levels at some critical postsynaptic receptors after acute activation of inhibitory autoreceptors, must be modulating the changes in agonistic behavior observed. Assuming this mechanism, additional postsynaptic antagonism in a drug (like S-15535) does not contribute additional effects. A compound like eltoprazine, which has (partial) 5-HT_{1A} and 5-HT_{1B} receptor agonistic effects would, after acute administration also switch off the firing of the 5-HT neuron (like alnespirone and S-15535) but additionally stimulate the 5-HT_{1B} receptor, still leading to specific anti-aggressive effects. This is presently puzzling and more research clearly has to be done including the status of the serotonergic system that contributes to all of the aspects that play a role in aggressive behavior. Is the serotonergic system in highly aggressive animals different from those of normal and low aggressive ones? This could be investigated by challenging high and low aggressive rats with dose ranges of selective, silent and non-discriminating (pre- versus post) 5-HT_{1A} receptor antagonists, like WAY-100,635. De Boer et al. (1999) describe, but unfortunately do not show, data that this overall silent antagonist (with regard to intrinsic effects on aggression) has differential effects on low (increase in aggression) versus high aggressive rats (decrease in aggression). This indicates differences in basal tone of the serotonergic systems in these rats with differences in basal aggression levels (traits) and supports the need to study the effects of complicated serotonergic compounds (like S-15535) in these different endophenotypes (cf. Van der Vegt et al., 2001). Studies of 5-HT_{1B} receptor agonists (eltoprazine, TFMPP, zolmitriptan, CP-94,253 and anpirtoline) have always found anti-aggressive effects, independent of the basal level of the animals (Mos et al., 1992; Miczek et al., 2002; Olivier and Mos, 1986; De Almeida and Miczek, 2002), again additional support for a postsynaptic mediated 5-HT_{1B} receptor agonism underlying the specific anti-aggressive effects. If presynaptic 5-HT_{1B} receptors were the mediators of this serenic effect, similar baseline aggression level effects should have been seen.

Chronic application (Mos et al., 1996) of the various 5-HT_{1A} and 5-HT_{1B} ligands should be extremely useful in delineating whether the acute anti-aggressive effects are indeed primarily induced by a receptor that has a very direct modulatory effect on

aggression (as postulated here for the postsynaptic 5-HT_{1B} receptor) or is due to indirect effects via manipulation of the firing capacities of the serotonergic neuron (5-HT_{1A} autoreceptor, 5-HT_{1B} presynaptic autoreceptor and serotonin transporter).

5-HT_{1B} receptor knockout mice (Saudou et al., 1994) show enhanced aggressive behavior (Saudou et al., 1994; Ramboz et al., 1995; Brunner and Hen, 1997; Bouwknecht et al., 2001), but due to the low baseline aggression level of the genetic background (129Sv) strain, the 'enhanced' aggression in the knockout mice was still low. More recent studies (Pattij et al., 2003, 2004; Bouwknecht et al., 2001) have implicated the 5-HT_{1B} receptor in impulsivity regulation, rather than offensive aggression per sé (Lesch and Merschdorf, 2000). Olivier et al. (1995) suggest that the specific anti-aggressive effects of 5-HT_{1B} receptor agonist are modulated via postsynaptic 5-HT_{1B} receptors. Such postsynaptic 5-HT_{1B} receptors are located as heteroreceptors on non-serotonergic neurons (including dopaminergic, cholinergic, and GAB_AA-ergic neurons). These heteroceptors, when activated by 5-HT_{1B} inhibit ongoing behavior, including aggression. Thus, 5-HT_{1B} receptor agonists inhibit those 'aggression or impulsivity' modulating neurons and removing postsynaptic 5-HT_{1B} receptors (via null mutation of the 5-HT_{1B} receptor gene) removes this 'brake', thereby facilitating various behaviors related to impulsivity, hyperactivity and aggression (Olivier and Young, 2002). Based on the 'hyper-aggressive' 5-HT_{1B} receptor knockout mouse and the anti-aggressive effects of 5-HT_{1B} receptor agonists, one could suggest that administration of 5-HT_{1B} receptor antagonists might lead to facilitation of aggression. However, all such antagonists appear silent, comparable to 5-HT_{1A} receptor antagonists, probably indicating that under normal, physiological conditions the serotonergic tone at postsynaptic 5-HT_{1B} receptors is not that strong.

One of the most remarkable findings is the absence of any anti-aggressive action HT_{1A} receptor agonists (8-OH-DPAT, flesinoxan, buspirone) in brain-stimulation induced aggression in the rat in a very distinct hypothalamic area (Kruk, 1991). Stimulation of this area induces offensive aggressive behavior that can be considered pathological, as it is induced in a situation that normally does not induce aggression whereas the opponents are not aware of any aggressive intentions of the attacker. This 'offensive aggression' area is clearly different from a 'defensive aggression' area needed to defend against attackers such as predators (Siegel et al., 1999). In contrast, 5-HT_{1B} receptor agonists, including eltoprazine, fluprazine and TFMPP (Kruk, 1991; Olivier et al., 1994; van der Poe1 et al., 1982) reduce this hypothalamic-induced attack dose-dependently, strongly supporting a postsynaptic site of action, presumably a pool of 5- HT_{1B} heteroreceptors on non-serotonergic neurons. In rats, attacks could be eleicited in this area when GABA antagonists, glutamate agonists or both were locally applied (Adams et al., 1993; Haller et al., 1998; Roeling et al., 1993). Glutamatergic and GABA-ergic systems are of particular interest, as they constitute the major excitatory and inhibitory systems, respectively, in the brain. Hrabovszky et al. (2005) found a remarkable similarity in the distribution of the hypothalamic attack area and glutamatergic cell groups, suggesting that these latter cells mediate the aggression induced by electrical stimulation. Moreover, GABA-ergic cells were also present in this 'aggression' area; dispersed between the glutamatergic cells. 5-HT_{1B} heteroreceptors are amongst others localized on GABA-ergic and glutamatergic cells (Sari, 2004) and this might be the simplest explanation of the potent anti-aggressive action of 5-HT_{1B} receptor agonists in this aggression paradigm. Whether these heteroreceptors exert their inhibitory function on glutamatergic or GABA-ergic neurons is unclear. When the serotonergic system is active, high levels of serotonin might activate the heteroreceptors on glutamatergic neurons, thereby inhibiting the activity of such neurons and leading to a decrease in aggression. This implicates that aggression (at least the hypothalamical part of it) is under serotonergic tone; low activity facilitates aggression, high activity inhibits it. In that way it can be understood that activation of somatodendritic 5-HT_{1A} autoreceptors in the hypothalamic aggression model does not have any effect on aggression levels, because the electrical stimulation overrules the disinhibitory effects of low serotonin levels. SSRIs that acutely enhance serotonin levels in the synaptic cleft (Adell et al., 2002) and thus would create a high-serotonin tone at the 5-HT_{1B} heteroreceptor should have anti-aggressive effects in the hypothalamic aggression model; this indeed has been found for fluvoxamine (Kruk, 1991; Olivier et al., 1990b). It can be postulated that hypothalamic aggression constitutes only the consummatory (final) part of the execution of aggression. By direct stimulation of the hypothalamic aggression area introductory elements normally acting during the complex behavioral, sensoric and motoric phases during all aspects of agonistic interactions, are overruled or even skipped. It could be postulated that the serotonergic system contributes both to the appetitive and consummatory phases of agonistic behavior; 5-HT_{1B} heteroreceptors play a role in the later phase, whereas others, including 5-HT_{1A} receptors have their function in the former phases.

3.2. Human evidence

Our hypothesis that the 5-HT_{1B} (hetero) receptor plays a vital role in modulation of consummatory aspects of offensive aggression also implies that altered function of this receptor in humans may contribute to (pathological) changes in aggressive behavior under various circumstances. The human 5-HT_{1B} receptor (HTRlB) is located at chromosome 6q14.1 and does not have introns. Many mutation scans have identified a number of polymorphisms in the coding sequence and surrounding 5′- and 3′-untranslated regions (UCR) and more than 20 association studies have been published with varying results (Sanders et al., 2002). A missense mutation G861C, a silent SNP, has often been used for the association studies and some interesting associations have been found using this polymorphism, including antisocial alcoholism (Lappalainen et al., 1998), history of suicide attempts (New et al., 2001) and obsessive compulsive disorder (Mundo et al., 2000). It has been found that subjects homozygous for G861C show an enhanced binding to the HTRIB; thereby indicating functional changes (Huang et al.,

1999). Other likely candidates that influence the functional activity of the 5-HT_{1B} receptor genes are functional SNPs in the regulatory (promoter) regions of the HTRlB. Some functional SNPs have been found (Duan et al., 2003) and they seem to be in linkage disequilibrium with the G861C marker: the latter has been associated with several psychiatric disorders, including pervasive aggressive children (Davidge et al., 2004), and antisocial behavior in alcoholics (Hasegawa et al., 2002; Soyka et al., 2004). Suicidal behavior and suicide, often considered inward-directed aggression were however, never associated with G861C polymorphism (Nishiguchi et al., 2001; Rujescu et al., 2003; Stefulj et al., 2004).

It is not at all clear however what the importance of these various polymorphisms in the promoter or coding regions of the HT_{1B} is: in our theory a decrease in function would induce enhanced aggression. Moreover, because the polymorphisms are present in the pre- and postsynaptic 5-HT_{1B} receptors, the functional consequences could be extremely complex.

Another candidate gene, indirectly influencing the activity at 5-HT_{1B} (hetero) receptors is the 5-HT transporter (5-HTT). Lowered serotonin levels at the 5-HT_{1B} heteroreceptor might lead to diminished activation of it and consequently to less inhibition of the postsynaptic neurons, leading to enhanced aggression. A functional polymorphism of the 5-HTT gene has been described, a 44-base pair insertion/deletion in the upstream regulatory promoter region (5-HTTLPR): two alleles are present: 'long' (L) and 'short' (S) ones (Heils et al., 1995). Moreover, a variable number of tandem repeats polymorphism (VNTR) in the second intron has been found (Ogilvie et al., 1996). The VNTR polymorphism consists of nine, 10 or 12 copies of a 16–17 base pair repeat element that may influence transcription of the 5-HTT gene (MacKenzie and Quinn, 1999). There are no studies into the relationship between the 5-HTT VNTR and aggression. This in contrast to the bi-allelic functional polymorphism in the promoter region, that affects 5-HTT-gene expression since the S promoter is less active than the L promoter, and SS genotypes express 50% of the 5-HTT-protein level of LL genotypes (Collier et al., 1996). The 5-HTTLPR polymorphism has been studied extensively in relation to personality and psychiatric disorders, and a number of studies have indicated that genotype of the 5-HTTLPR allele is associated with various anxiety- and depression related personality traits (van Gestel and van Broeckhoven, 2003; Schinka et al., 2004). Several studies have found associations between aggression and violence and the S- alleles of the 5-HTTLPR, e.g., in extremely violent crime in Chinese males (Liao et al., 2004), in forensic psychiatric violent Caucasian males (Retz et al., 2004), in suicidal behavior (Anguelova et al., 2003; Arango et al., 2003; Bellivier et al., 2000; Caspi et al., 2003), in aggressive children (Davidge et al., 2004), and in impulsivity (Lee et al., 2003). Because such studies are based on associations and not on direct causality the result have to be considered extremely careful. Nevertheless, the data seem in line with our hypothesis that lower 5-HT activity somehow can be associated with enhanced aggression and violence.

No specific drugs are available for treatment of aggression or violence in humans, in particular acting via 5-HT_{1B} receptors. Although some anti-migraine triptans (notably zolmitriptan and sumatriptan) can be applied in patients, no well-designed and controlled studies with these compounds have been performed in the realm of potential anti-aggressive activity. It would be highly interesting to see whether such compounds indeed might reduce aggression, as suggested by animal studies (de Almeida et al., 2001). Selective serotonin re-uptake inhibitors (SSRIs) seem to exert some anti-aggressive effects (Cherek et al., 2002; Coccaro and Kavoussi, 1997) but most studies are performed in psychiatric patients where aggression was co-morbid, e.g., in depression or anxiety disorders (Walsh and Dinan, 2001) Again, SSRIs have never been tested on their primary anti-aggressive potential in patients with aggression or violence as primary indication. Animal studies suggest that SSRIs might have some, but limited anti-aggressive action, in aggressive or violent patients.

4. Conclusions

The serotonergic system in the CNS has complex interactions with many, if not all other neurotransmitter systems in the brain. Its localization, distribution and amazing receptor diversity makes it an appealing system for modulatory functions in many basic behaviors, including e.g., food and water intake, sexual behavior, aggression and many more. Notwithstanding decades of research into the putative role of the serotonergic system in aggression, no clear picture has emerged thus far. The 5-HT system seems, dependent on state or trait, to be involved in either the performance or the termination of aggressive behaviors. The present technology appears not developed enough to give answers to these questions. Application of drugs, and particular selective ligands for certain subtype receptors, seems a more promising approach to unraveling the role of 5-HT in aggression. The (postsynaptic) 5-HT_{1B} and to a lesser extent, the 5-HT_{1A} receptor seems to play a prominent role, at least in rodents, in the modulation of (offensive) aggression. Although association studies can only indirectly support causal linkage between serotonergic activity and aggression, such studies in humans indicate some support for 5-HT_{1B} receptors and serotonin transporters in such a connection.

References

Adams, D.B., Boudreau, W., Cowan, C.W., Kokonowski, C., Oberteuffer, K., Yohay, K., 1993. Offense produced by chemical stimulation of the anterior hypothalamus of the rat. Physiol. Behav. 53, 1127–1132.

Adell, A., Celada, P., Abellan, M.T., Artigas, F., 2002. Origin and functional role of the extracellular serotonin in the midbrain raphe nuclei. Brain Res. Rev. 39, 154–180.

Adham, N., Romanienko, P., Hartig, P., Weinshank, R.L., Branchek, T., 1992. The rat 5-hydroxytryptamine 1B receptor is the species homologue of the human 5-hydroxytryptamine 1B beta receptor. Mol. Pharmacol. 41, 1–7.

Anguelova, M., Benkelfat, C., Turecki, G., 2003. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. Mol. Psychiatry 8, 646–653.

Arango, V., Huang, Y., Underwood, M.D., Mann, J.J., 2003. Genetics of the serotonergic system in suicidal behavior. J. Psychiatr. Res. 37, 375–386.

Beck, S.G., Pan, Y.-Z., Akanwa, A.C., Kirby, L.G., 2004. Median and dorsal raphe neurons are not electrophysiologically identical. J. Neurophysiol. 91, 994–1005.

Bellivier, F., Szoke, A., Henry, C., Lacoste, J., Bottos, C., Nosten-Bertrand, M., Hardy, P., Rouillon, F., Launay, J.-M., Laplanche, J.-P., Leboyer, M., 2000. Possible association between serotonin transporter gene polymorphism and violent suicidal behavior in mood disorders. Biol. Psychiatry 48, 319–322.

Bonaventura, P., Voorn, P., Luyten, W.H.M.L., Jurzak, M., Schotte, A., Leyten, J.E., 1998. Detailed mapping of serotonin 5-HT_{1B} and 5-HT_{lD} receptor messenger RNA and ligand binding sites in guinea pig brain and trigeminal ganglion: clues for function. Neuroscience 82, 469–484.

Boschert, U., Amara, D.A., Segu, L., Hen, R., 1994. The mouse 5-hydroxytryptaminelB receptor is localized predominantly on axon terminals. Neuroscience 58, 67–182.

Boulenguez, P., Pinard, R., Segu, L., 1996. Subcellular localization of 5-HT_{1B} binding sites in the striatum griseum superficiale of the rat superior colliculus: an electron microscopic quantitative autoradiographic study. Synapse 24, 203–212.

Bouwknecht, J.A., Hijzen, T.H., Van der Gugten, J., Maes, R.A.A., Hen, R., Olivier, B., 2001. Absence of 5-HT_{1B} receptors is associated with impaired motor impulse control in male 5-HT_{lB} knockout mice. Biol. Psychiatry 49, 557–568.

Bradford, L.D., Olivier, B., Van Dalen, D., Schipper, J., 1984. Serenics: the pharmacology of fluprazine and DU 28412. In: Miczek, K.A., Kruk, M.R., Olivier, B. (Eds.), Ethopharmacological Aggression Research. Alan R. Liss Inc., New York, N.Y., pp. 191–208.

Brown, G.L., Goodwin, F.K., Ballenger, J.C., Goyer, P.F., Major, L.F., 1979. Aggression in humans: correlates with cerebrospinal fluid amine metabolites. Psychiatry Res. 1, 131–139.

Brunner, D., Hen, R., 1997. Insights into the neurology of impulsive behavior from serotonin receptor knockout mice. Ann. N.Y. Acad. Sci. 836, 81–105.

Bruinvels, A.T., Palacios, J.M., Hoyer, D., 1993. Autoradiographic characterization and localization of 5-HT_{1D} compared to 5-HT_{1B} binding sites in the rat brain. Naunyn-Schmiedeberg's Arch. Pharmacol. 347, 569–582.

Bruinvels, A.T., Landwehrmeyer, B., Gustafson, E.L., Durkin, M.M., Mengod, G., Branchek, T.A., Hoyer, D., Palacios, J.M., 1994. Localization of 5-HT_{lB}, 5-$HT_{1D\ alpha}$, 5-HT_{1E} and 5-HT_{1F} receptor messenger RNA in rodent and primate brain. Neuropharmacology 33, 367–386.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.A., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.

Chen, H.T., Clark, M., Goldman, D., 1992. Quantitative autoradiography of [^{3}H] paroxetine binding sites in rat brain. J. Pharmacol. Toxicol. Methods 27, 209–216.

Cherek, D.R., Lane, S.D., Pietras, C.J., Steinberg, J.L., 2002. Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. Psychopharmacology 159, 266–274.

Coccaro, E.F., 1989. Central serotonin and impulsive aggression. Br. J. Psychiatry 155, 52–62.

Coccaro, E.F., Kavoussi, R.J., 1997. Fluoxetine and impulsive aggressive behavior in personality disordered subjects. Arch. Gen. Psychiatry 54, 1081–1088.

Collier, D.A., Stober, G., Li, T., Heils, A., Catalano, M., Di Bella, D., Arranz, M. J., Murray, R.M., Vallada, H.P., Bengel, D., Muller, C.R., Roberts, G.W., Smeraldi, E., Kirov, G., Sham, P., Lesch, K.P., 1996. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol. Psychiatry 1, 453–460.

D'Amato, R.J., Largent, B.L., Snowman, A.M., Snyder, S.H., 1987. Selective labelling of serutonin uptake sites in rat brain by [^{3}H]-citalopram contrasted to labelling of multiple sites by [^{3}H]-imipramine. J. Pharmacol. Exp. Ther. 112, 121–128.

Davidge, K.M., Atkinson, L., Douglas, L., Lee, V., Shapiro, S., Kennedy, J.L., Beitchman, J.H., 2004. Association of the serotonin transporter and 5-$HT_{lD\beta}$ receptor genes with extreme, persistent and pervasive aggressive behaviour in children. Psychiatr. Genet. 14, 143–146.

de Almeida, R.M.M., Nikulina, E., Faccidomo, S., Fish, E., Miczek, K.A., 2001. Zolmitriptan, a 5-$HT_{lB/lD}$ receptor agonist, alcohol, and aggression in male mice. Psychopharmacology 157, 131–141.

De Almeida, R.M.M., Miczek, K.A., 2002. Aggression escalated by social instigation or by discontinuation of reinforcement ('frustration') in mice: inhibition by anpirtoline—a 5-HT_{1B} receptor agonist. Neuropsychopharcamacology 272, 171–181.

De Boer, S.F., Lesourd, M., Mocaër, E., Koolhaas, J.M., 1999. Selective antiaggressive effects of alnespirone in resident–intruder test are mediated via 5-hydroxytryptamine$_{lA}$ receptors: a comparative pharmacological study with 8-hydroxy-2-dipropylaminotetralin, ipsapirone, buspirone, eltoprazine, and WAY-100635. J. Pharmacol. Exp. Ther. 288, 1125–1133.

De Boer, S.F., Lesourd, M., Mocaër, E., Koolhaas, J.M., 2000. Somatodendritic 5-HT_{1A} autoreceptors mediate the anti-aggressive actions of 5-HT_{1A} receptor agonists in rats: an ethopharmacological study with S-15535, alnespirone, and WAY-100635. Neuropsychopharmacology 23, 20–33.

de Boer, S.F., Van der Vegt, B.J., Koolhaas, J.M., 2003. Individual variation in aggression of feral rodent strains: a standard for the genetics of aggression and violence? Behav. Genet. 33, 485–501.

Doucet, E., Pohl, M., Fattaccini, C.M., Adrien, J., Mestikawy, S.E., Hamon, M., 1995. In situ hybridization evidence for the synthesis of 5-HT_{1B} receptor in serotonergic neurons of anterior raphe nuclei in the rat brain. Synapse 19, 18–28.

Duan, J., Sanders, A.R., Vander Molen, J.E., Martinolich, L., Mowry, B.J., Levinson, D.F., Crowe, R.R., Silverman, J.M., Gejman, P.V., 2003. Polymorhisms in the 5'-untranslated region of the human serotonin receptor 1B (HTR1B) gene affects gene expression. Mol. Psychiatry 8, 901–910.

Engel, G., Göthert, M., Hoyer, D., Schlicker, E., Hillenbrand, K., 1986. Identity of inhibitory presynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT_{lB} binding sites. Naunyn-Schmiedeberg's Arch. Pharmacol. 332, 1–7.

Ferrari, P.F., van Erp, A.M.M., Tornatzky, W., Miczek, K.A., 2003. Accumbal dopamine and serotonin in anticipation of the next aggressive episode in rats. Eur. J. Neurosci. 17, 371–378.

Fish, E.W., Faccidomo, S., Miczek, K.A., 1999. Aggression heightened by alcohol or social instigation in mice: reduction by the 5-HT_{1B} receptor agonist CP-94, 253. Psychopharmacology 146, 391–399.

Giacalone, E., Tansella, M., Valzelli, L., Garattini, S., 1968. Brain serotonin metabolism in isolated aggressive mice. Biochem. Pharmacol. I7, 1315–1327.

Göthert, M., Propping, P., Bonisch, H., Bruss, M., Nothen, M.M., 1998. Genetic variation in human 5-HT_5 receptors: potential pathogenetic and pharmacological role. Ann. N.Y. Acad. Sci. 861, 26–30.

Haller, J., Abraham, I., Zelena, D., Juhasz, G., Makara, G.B., Kruk, M.R., 1998. Aggressive experience affects the sensitivity of neurons towards pharmacological treatment in the hypothalamic attack area. Behav. Pharmacol. l9, 469–475.

Hamblin, M.W., Metcalf, M.A., McGuffin, R.W., Karpells, S., 1992. Molecular cloning and functional characterization of a human 5-HT_{1B} serotonin receptor: a homologue of the rat 5-HT_{1B} receptor with 5-HT_{1D}-like pharmacological specificity. Biochem. Biophys. Res. Commun. 184, 752–759.

Hasegawa, Y., Higuchi, S., Matsushita, S., Miyaoka, H., 2002. Association of a polymorphism of the serotonin 1B receptor gene and alcohol dependence with inactive aldehyde dehydrogenase-2. J. Neural Transm. 109, 513–521.

Hartig, P.R., Hoyer, D., Humphrey, P.P., Martin, G.R., 1996. Alignment of receptor nomenclature with the human genome: classification of 5-HT_{1B} and 5-HT_{lD} receptor subtypes. Trends Pharmacol. Sci. 17, 103–105.

Heils, A., Teufel, A., Petri, S., Seemann, M., Bengel, D., Balling, U., Riederer, P., Lesch, K.P., 1995. Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. J. Neural Transm. Gen. Sect. 102, 247–254.

Hoffman, B., 1993. Molecular biology of serotonin uptake sites. In: Van Houtte, P., Saxena, P.R., Paoletti, R., Brunello, N., Jackson, A.S. (Eds.), Serotonin—From Cell Biology to Pharmacology and Therapeutics. Kluwer Academic, Dordrecht, pp. 9–19.

Hrabovszky, E., Halász, J., Meelis, W., Kruk, M.R., Liposits, Z.S., 2005. Neurochemical characterization of hypothalamic neurons involved in attack behaviour: glutamatergic dominance and co-expression of thyrotropin-releasing hormone in a subset of glutamatergic neurons. Neuroscience 133, 657–666.

Hrdina, P.B., Foy, B., Hepner, A., Summers, R.J., 1990. Antidepressant binding sites in brain: autoradiographic comparison of [^{3}H]paroxetine and [^{3}H]imipramine localization and relationship to serotonin transporter. J. Pharmacol. Exp. Ther. 252, 410–418.

Huang, Y.Y., Grailhe, R., Arango, V., Hen, R., Mann, J.J., 1999. Relationship of psychopathology to the human serotonin 1B genotype and receptor binding kinetics in post-mortem brain tissue. Neuropsychopharmacology 21, 238–246.

Jacobs, B., Azmitzia, E., 1992. Structure and function of the brain serotonin system. Physiol. Rev. 72, 165–229.

Jin, H., Oksenberg, D., Ashkenazi, A., Peroutka, S.J., Duncan, A.M., Rozmahel, R., Yang, Y., Mengod, G., Palacios, J.M., O'Dowd, B.F., 1992. Characterization of the human 5-hydroxytryptamine 1B receptor. J. Biol. Chem. 267, 5735–5738.

Kruesi, M.J.P., Rapoport, J.L., Hamburger, S., Hibbs, E., Potter, W.Z., Lenane, M., Brown, G.R., 1990. Cerebrospinal fluid monoamine metabolites, aggression, and impulsivity in disruptive behavior disorders of children and adolescents. Arch. Gen. Psychiatry 47, 419–426.

Kruk, M.R., 1991. Ethology and pharmacology of hypothalamic aggression in the rat. Neurosci. Biobehav. Rev. 15, 527–538.

Kruk, M.R., van der Poel, A.M., de Vos-Frerichs, T.P., 1979. The induction of aggressive behaviour by electrical stimulation in the hypothalamus of male rats. Behaviour 70, 292–322.

Kusjlic, S., Copolov, D.L., van den Buuse, M., 2003. Differential role of serotonergic projections arising from the dorsal and median raphe nuclei in locomotor hyperactivity and prepulse inhibition. Neuropsychopharmacology 28, 2138–2147.

Lammers, J.H., Kruk, M.R., Meelis, W., van der Poel, A.M., 1988. Hypothalamic substrates for brain stimulation-induced attack, teeth-chattering and social grooming in the rat. Brain Res. 449, 311–327.

Lappalainen, J., Long, J.C., Eggert, M., Ozaki, N., Robin, R.W., Brown, G.L., Naukkarinen, H., Virkkunen, M., Linnoila, M., Goldman, D., 1998. Linkage of antisocial alcoholism to the serotonin 5-HT$_{1B}$ receptor gene in 2 populations. Arch. Gen. Psychiatry 55, 989–994.

Lee, J.-H., Kim, H.-T., Hyun, D.-S., 2003. Possible association between serotonin transporter promoter region polymorphism and impulsivity in Koreans. Psychiatry Res. 118, 19–24.

Lesch, K.P., Merschdorf, U., 2000. Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. Behav. Sci. Law 18, 581–604.

Liao, D.-L., Hong, C.-J., Shih, H.-L., Tsai, S.-J., 2004. Possible association between serotonin transporter promoter region polymorphisms and extremely violent crime in Chinese males. Neuropsychobiology 50, 284–287.

Linnoila, M., Virkkunen, M., Scheinin, M., Nuutila, A., Rimon, R., Goodwin, F. K., 1983. Low cerebrospinal fluid 5-hydroxyindole-acetic acid concentration differentiates impulsive from non-impulsive violent behaviour. Life Sci. 33, 2609–2614.

MacKenzie, A., Quinn, J., 1999. A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc. Natl. Acad. Sci. U. S. A. 96, 15251–15255.

Mann, J.J., 2003. Neuobiology of suicidal behaviour. Nat. Rev. Neurosci. 4, 819–828.

Maroteaux, L., Saudou, F., Amlaiky, N., Boschert, U., Plassat, J.L., Hen, R., 1992. Mouse 5-HT$_{1B}$ serotonin receptor: cloning, firnctional expression, and localization in motor control centers. Proc. Natl. Acad. Sci. U. S. A. 89, 3020–3024.

Maura, G., Raiteri, M., 1986. Cholinergic terminals in rat hippocampus possess 5-HT$_{IB}$ receptors mediating inhibition of acetylcholine release. Eur. J. Pharmacol. 129, 333–337.

Metcalf, M.A., McGuffin, R.W., Hamblin, M.W., 1992. Conversion of the human 5-HT$_{1D}$ beta serotonin receptor to the rat 5-HT$_{1B}$ ligand-binding phenotype by Thr355Asn site directed mutagenesis. Biochem. Pharmacol. 44, 1917–1920.

Miczek, K.A., Barros, H.M., Sakoda, L., Weerts, E.M., 1998a. Alcohol and heightened aggression in individual mice. Alcohol Clin. Exp. Res. 22, 1698–1705.

Miczek, K.A., Hussain, S., Faccidomo, S., 1998b. Alcohol-heightened aggression in mice: attenuation by 5-HT$_{1A}$ receptor agonists. Psychopharmacology 139, 160–168.

Miczek, K.A., de Almeida, R.M.M.A., 2001. Oral drug self-administration in the home cage of mice: alcohol-heightened aggression and inhibition by the 5-HT$_{1B}$ agonist anpirtoline. Psychopharmacology 157, 421–429.

Miczek, K.A., Fish, E.W., de Bold, J.F., de Almeida, R.M.M., 2002. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and y-aminobutyric acid systems. Psychopharmacology 163, 434–458.

Millan, M.J., Rivet, J.-M., Canton, H., Lejeune, F., Gobert, A., Widdowson, P., Bervoets, K., Brocco, M., Peglion, J.-L., 1993. S-15535: a highly selective benzodioxopiperazine 5-HT$_{1A}$ receptor ligand which acts as an agonist and an antagonist at presynaptic and postsynaptic sites respectively. Eur. J. Pharmacol. 230, 99–102.

Millan, M.J., Canton, H., Gobert, A., Lejeune, F., Rivet, J.-M., Bervoets, K., Brocco, M., Widdowson, P., Mennini, T., Audinot, V., Honore, P., Renouard, A., Le Marouille-Girardon, S., Verriele, L., Gressier, H., Peglion, J.-L., 1994. Novel benzodioxopiperazines acting as antagonists at postsynaptic 5-HT$_{1A}$ receptors and as agonists at 5-HT$_{1A}$ autoreceptors: a comparative pharmacological characterization with proposed 5-HT$_{1A}$ antagonists. J. Pharmacol. Exp. Ther. 268, 337–352.

Millan, M.J., Hjorth, S., Samanin, R., Schreiber, R., Jaffard, R., De Ladonchamps, B., Veiga, S., Goument, B., Peglion, J.-L., Spedding, M., Brocco, M., 1997. S-15535, a novel benzodioxopiperazine ligand of serotonin (5-HT) 1A receptors: II. Modulation of hippocampal serotonin release in relation to potential anxiolytic properties. J. Pharmacol. Exp. Ther. 282, 148–161.

Mos, J., Olivier, B., Poth, M., van Aken, H., 1992. The effects of intraventricular administration of eltoprazine, l-(3-trifluoromethylphenyl) piperazine hydrochloride and 8-hydroxy-2-(di-*n*-propylamino) tetralin on resident intruder aggression in the rat. Eur. J. Pharmacol. 212, 295–298.

Mos, J., Olivier, B., Poth, M., van Oorschot, R., Van Aken, H., 1993. The effects of dorsal raphe administration of eltoprazine, TF and lPP and 8-OH-DPAT on resident intruder aggression in the rat. Eur. J. Pharmacol. 238, 411–415.

Mos, J., Van Aken, H.M.E., Van Oorschot, R., Olivier, B., 1996. Chronic treatment of the serenic eltoprazine does not lead to tolerance in its anti-aggressive action in rats. Eur. Neuropsychopharmacol. 6, 1–7.

Mundo, E., Richter, M.A., Sam, F., Macciardi, F., Kennedy, J.L., 2000. Is the 5-HT (1Dbeta) receptor gene implicated in the pathogenesis of obsessive–compulsive disorder? Am. J. Psychiatry 157, 1160–1161.

New, A.S., Gelernter, J., Goodman, M., Mitropoulou, V., Koenigsberg, H., Silverman, J., Siever, L.J., 2001. Suicide, impulsive aggression, and HTRIB genotype. Biol. Psychiatry 50, 62–65.

Nishiguchi, N., Shirakawa, O., Ono, H., Nishimura, A., Nushida, H., Ueno, Y., Maeda, K., 2001. No evidence of an association between 5-HT$_{1B}$ receptor gene polymorphism and suicide victims in a Japanese population. Am. J. Med. Genet. 105, 343–345.

Ogilvie, A.D., Battersby, S., Bubb, V.J., Fink, G., Harmar, A.J., Goodwim, G.M., Smith, C.A., 1996. Polymorphism in serotonin transporter gene associated with susceptibility to major depression. Lancet 347, 731–733.

Oksenberg, D., Marsters, S.A., O'Dowd, B.F., Jin, H., Havlik, S., Peroutka, S.J., Ashkenasi, A., 1992. A single amino-acid difference confers major pharmacological variation between human and rodent 5-HT$_{1B}$ receptors. Nature 360, 161–163.

Olivier, B., 1981. Selective anti-aggressive properties of DU 27725: ethological analyses of intermale and territorial aggression in the rat. Pharmacol. Biochem. Behav. 14 (supp1), 61–77.

Olivier, B., Mos, J., 1986. Serenics and aggression. Stress Med. 197–209.

Olivier, B., van Dalen, D., 1982. Social behaviour in rats and mice. Aggress. Behav. 8, 163–166.

Olivier, B., Young, L., 2002. Animal models of aggression. In: Davis, K.L., Charney, D., Coyle, J.T., Nemeroff, C. (Eds.), Neuropsychopharmacology:

The 5th Generation of Progress. Williams and Wilkins, Lippincott, pp. 1699–1708.

Olivier, B., Mos, J., van der Poel, A.M., Krijzer, F.N.C., Kruk, M.R., 1984. Effect of a new psychoactive drug (DU 27716) on different models of agonistic behaviour and EEG. In: Flannelly, K.J., Blanchard, R.J., Blanchard, D.C. (Eds.), Biological Perspectives on Aggression. Alan R. Liss, New York, pp. 261–279.

Olivier, B., Van Dalen, D., Hartog, J., 1986. A new class of psychotropic drugs: serenics. Drugs Future 11, L473–L494.

Olivier, B., Mos, J., Van der Heyden, J., Hartog, J., 1989. Serotonergic modulation of social interaction in male mice. Psychopharmacology 97, 154–156.

Olivier, B., Mos, J., Hartog, J., Rasmussen, D.L., 1990a. Serenics: a new class of drugs for putative selective treatment of pathological destructive behaviour. Drug News Persp. 3, 261–271.

Olivier, B., Mos, J., Rasmussen, D., 1990b. Behavioural pharmacology of the serenic eltoprazine. Rev. Drug Metabol. Drug Interact. 8, 31–83.

Olivier, B., Mos, J., Raghoebar, M., de Koning, P., Mak, M., 1994. Serenics. Prog. Drug Res. 42, 167–308.

Olivier, B., Mos, J., van Oorschot, R., Hen, R., 1995. Serotonin receptors and animal models of aggressive behaviour. Pharmacopsychiatry 28, 80–90.

Pattij, T., Van der Linde, J., Groenink, L., Broersen, L., Van der Gugten, J., Maes, R.A.A., Olivier, B., 2003. Operant learning and differential-reinforcement-of-low-rate 36-sec responding in 5-HT_{1A} and 5-HT_{1B} receptor knockout mice. Behav. Brain Res. 141, 137–145.

Pattij, T., Broersen, L., Olivier, B., 2004. Impulsive-like responding in differential-reinforcement-of-low-rate 36-sec responding in mice depends on training history. Neurosci. Lett. 354, 169–171.

Pazos, A., Palacios, J.M., 1985. Quantitative autoradiographic mapping of serotonin receptors in the rat brain I. Serotonin-1 receptors. Brain Res. 346, 205–230.

Pineÿro, G., Blier, P., 1999. Autoregulation of serotonin neurons: role in antidepressant drug action. Pharmacol. Rev. 51, 533–591.

Ramboz, S., Saudou, F., Amara, D.A., Belzung, C., Segu, L., Misslin, R., Buhot, M.C., Hen, R., 1995. 5-HT_{1D} receptor knock out-behavioral consequences. Behav. Brain Res. 73, 305–312.

Retz, W., Retz-Juninger, P., Supprian, T., Thome, J., Rösler, M., 2004. Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorder, impulsivity, and childhood ADHD psychopathology. Behav. Sci. Law 22, 415–425.

Roeling, T.A., Kruk, M.R., Schuurmans, R., Veening, J.G., 1993. Behavioural responses of bicuculline methiodide injections into the ventral hypothalamus of freely moving, socially interacting rats. Brain Res. 615, 121–127.

Rujescu, D., Giegling, I., Sato, T., Möller, H.-J., 2003. Lack of association between serotonin 5-HT_{1B} receptor gene polymorphism and suicidal behaviour. Am. J. Med. Genet., B 116B, 69–71.

Sanders, A.R., Duan, J., Gejman, P.V., 2002. DNA variation and psychopharmacology of the human serotonin receptor 1B (HTRlB) gene. Pharmacogenomics 3, 745–762.

Sari, Y., 2004. Serotonin$_{1B}$ receptors: from protein to physiological function and behaviour. Neurosci. Biobehav. Rev. 28, 565–582.

Sari, Y., Miquel, M.C., Brisorgueil, M.J., Ruiz, G., Doucet, E., Hamon, M., Vergé, D., 1999. Cellular and subcellular localization of 5-hydroxytryptaminelB receptors in the rat central nervous system: immunocytochemical, autoradiographic and lesion studies. Neuroscience 88, 899–915.

Saudou, F., Amara, D.A., Dierich, A., Lemeur, M., Ramboz, S., Segu, L., Buhot, M.C., Hen, R., 1994. Enhanced aggressive behavior in mice lacking 5-HT_{1B} receptor. Science 265, 1875–1878.

Schinka, J.A., Busch, R.M., Robichaux-Keene, N., 2004. A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. Mol. Psychiatry 9, 197–202.

Siegel, A., Roeling, T.A.P., Gregg, T.R., Kruk, M.R., 1999. Neuropharmacology of brain-stimulation-evoked aggression. Neurosci. Biobehav. Rev. 23, 359–389.

Sijbesma, H., Schipper, J., de Kloet, E.R., Mos, J., van Aken, H., Olivier, B., 1991. Postsynaptic 5-HT_1 receptors and offensive aggression in rats: a combined behavioural and autoradiographic study with eltoprazine. Pharmacol. Biochem. Behav. 38, 447–458.

Soyka, M., Preuss, U.W., Koller, G., Zill, P., Bondy, B., 2004. Association of 5-HT_{1B} receptor gene and antisocial behaviour in alcoholism. J. Neural Transm. 111, 101–109.

Stefulj, J., Büttner, A., Skavic, J., Zill, P., Balija, M., Eisenmenger, W., Bondy, B., Jernej, B., 2004. Serotonin 1B (5-HT_{1B}) polymorphism (G861C) in suicide victims: association studies in German and Slavic population. Am. J. Med. Genet. 127B, 48–50.

Törk, I., 1990. Anatomy of the serotonergic system. Ann. N.Y. Acad. Sci. 90, 9–35.

van der Poel, A.M., Olivier, B., Mos, J., Kruk, M.R., Meelis, W., van Aken, J.H. M., 1982. The anti-aggressive effect of a new phenylpiperazine compound (DU27716) on hypothalamically induced behavioural activities. Pharmacol. Biochem. Behav. 17, 147–153.

Van der Vegt, B.J., de Boer, S.F., Buwalda, B., de Ruiter, A.J., de Jong, J.G., Koolhaas, J.M., 2001. Enhanced sensitivity of postsynaptic serotonin-1A receptors in rats and mice with high trait aggression. Physiol. Behav. 74, 205–211.

Van der Vegt, B.J., Lieuwes, N., Cremers, T.I.F.H., De Boer, S.F., Koolhaas, J. M., 2003. Cerebrospinal fluid monoamine and metabolic concentrations and aggression in rats. Horm. Behav. 44, 199–208.

Van Erp, M.M., Miczek, K.A., 2000. Aggressive behavior, increased accumbal dopamine and decreased cortical serotonin in rats. J. Neurosci. 15, 9320–9325.

van Gestel, S., van Broeckhoven, C., 2003. Genetics of personality: are we making progress? Mol. Psychiatry 8, 840–852.

Voigt, M.M., Laurie, D.J., Seeburg, P.H., Bach, A., 1991. Molecular cloning and characterization of a rat brain cDNA encoding a 5-hydroxytryptaminelB receptor. EMBO J. 10, 4017–4023.

Walsh, M.-T., Dinan, T.G., 2001. Selective serotonin reuptake inhibitors and violence: a review of the available evidence. Acta Psychiatr. Stand. 104, 84–91.

Zifa, E., Fillion, G., 1992. 5-hydroxytryptamine receptors. Pharmacol. Rev. 44, 401–458.