FUNCTIONAL BRAIN IMAGING OF SEROTONIN-2A RECEPTORS IN IMPULSIVE DOGS: A PILOT STUDY

Functionele beeldvorming van serotonine-2A receptoren in de hersenen van impulsief-agressieve honden

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ABSTRACT

Impulsive, disinhibited behavior in dogs, which comes to expression as aggression, has a major impact on public health. Measures taken without a real understanding of the underlying pathology are unlikely to be effective. It would therefore be not only of pathophysiological but also of clinical relevance to develop a research paradigm to investigate this aberrant behavior in dogs. The first aim of this article is to review the literature concerning functional-anatomical and biochemical research on animal impulsivity. On the basis of this research, a hypothesis involving the prefrontal serotonin-2A receptor in the frontal cortex is generated and the feasibility of quantifying the 5-HT2A receptor with Single Photon Emission Computed Tomography (SPECT) and the highly selective receptor radioligand ^{123}I-5I-R91150 is presented in a pilot study. If confirmed, this hypothesis may lead to the development of an in vivo research tool for investigating behavioral disorders and a modality for monitoring the effects of pharmacologic interventions and behavior therapy.

SAMENVATTING

Agressief, impulsief gedrag bij de hond heeft de laatste jaren voor ophef gezorgd omwille van een aantal dodelijke incidenten en wordt beschouwd als een niet onbelangrijk probleem voor het publieke welzijn. Een objectieve, meetbare, onderzoeksmodaliteit voor het onderzoek naar de pathofysiologie van dit afwijkend gedrag en, naar de toekomst toe, voor de klinische evaluatie van gedragsgestoorde honden, zou een aandeel kunnen hebben in meer gefundeerde overheidsmaatregelen. In dit artikel wordt een literatuuroverzicht gegeven betreffende het functioneel-anatomische en biochemische onderzoek van impulsief gedrag bij het dier. Er wordt een onderzoeksmodel voorgesteld waarbij de 5-HT2A receptor in beeld wordt gebracht met behulp van functionele beeldvorming gebruik makend van "single photon emission tomography" (SPET). De bevestiging van deze hypothese biedt de mogelijkheid om gedragsafwijkingen *in vivo* te onderzoeken en het effect van therapeutische interventies, medicamenteuze behandeling en gedragstherapie op een objectieve, meetbare manier te evalueren.

INTRODUCTION

Definition and classification of aggressive and impulsive behavior

In the literature, there is a striking lack of agreement on definitions and concepts related to aggression and impulsivity. A variety of experts possessing a wide range of expertise, including ethologists, zoologists, veterinarians and law enforcement officials, are involved in the study of aggressive and violent behavior, each with their own viewpoint and own operant definition and classification.

Aggression in animal research can be defined as "a manifestation of competition, the active demand by two or more individuals for a common limited resource, such as food, reproduction (access to mating), or territory". In this context, predatory aggression, intermale aggression, maternal aggression and territorial aggression are described. These types of behaviors are inborn and instinctive in nature and hence are not deviant, although they can be beyond control. The domestication of animals included the acceptance of these types of animal aggression by humans. The aggressive behavior of the animal is considered normal and is tolerated as long as it is appropriate in relation to the environmental conditions and stimuli.

Disinhibition and *impulsivity* in human research are defined as "acts related to inadequate self-control or impaired impulse-control". In animal research, impulsivity is related to the "incapacity to wait or to delay response". The "inappropriateness" of impulsive behavior can be illustrated by the literal definition of the word impulse as "a sudden spontaneous inclination or incitement to some usually unpremeditated action". Since this impulsive and disinhibited behavior is inappropriate and difficult to foresee compared to more predictable and "appropriate" aggressive behavior, it is more threatening and must therefore serve as a focus for treatment. Moreover, and beyond the academic discussion of the most correct term, this inappropriate "impulsive behavior", often aggressive in nature, seems to have a different biological basis in comparison with the appropriate "aggressive behavior". Since human biological psychiatric research offers an acceptable research hypothesis regarding impulsive behavior, which is often but not always violent in nature, the research strategy described in this article is directed toward the study of "impulsive animal subjects" and not toward "highly aggressive" ones that display no impulsivity.

Anatomical brain-behavior relationships in aggression and impulsivity

As a general conclusion of anatomical studies, both subcortical and cortical brain regions were found to be involved in aggression and impulsivity. Initially based on ablation and stimulation studies in animals, the model of aggressive drive (driven by the subcortical limbic system) and supervisory inhibition (directed by the (pre)frontal cortex) proposed in the period from the 1930s to the 1960s, has been further developed and refined up to the present.

In this model, the *limbic system* can be considered a primitive system that is directed towards survival, where unrefined feelings are generated and pleasant versus unpleasant emotions are discriminated. It is composed of the hypothalamus, the amygdala, the hippocampus, the septal nuclei and the anterior cingulate gyrus. The *hypothalamus* is the central core from which all emotions derive their motive force, though the emotional states that are elicited in the hypothalamus are very primitive (pleasant versus unpleasant), undirected (reflexive) and unrefined (on/off manner), and they seem to provide the immediate discharge of tensions in an almost reflexive manner, without concern for or understanding of its consequences. For instance, stimulation of the lateral hypothalamus induced extremes in emotionality, including intense attacks of rage accompanied by biting and attack upon any moving object. If the hypothalamic nucleus is destroyed, aggressive and attack behavior is abolished. In contrast to the primitive hypothalamus, the more recently developed *amygdala* is pre-eminent in the control and mediation of all higher-order emotional and motivational activities, including aggression. Firstly, it is able to modulate and even control rudimentary emotional forces governed by the hypothalamus. Secondly, the amygdala, via environmental surveillance, can discover a potentially threatening stimulus, and then act to excite and drive the hypothalamus to take appropriate action. The role of the amygdala is thought to be necessary for the animal's selection of aggressive (or submissive) behavior that is appropriate for a given social situation , and lesions disrupt the ability of the animal to conform its aggressive (or submissive) behavior to established social norms.

On the other hand, already in the third decade of the twentieth century the *prefrontal cortex* had been identified as being involved in the behavioral inhibition of drives. This finding was based on the observation of an abnormal voracity and aggressiveness in animals with large frontal lesions. These ablation studies had far more than a passing historical significance since the early reports in which "placidity" in primates after frontal lesions was described, led to the common neurosurgical practice of Egas Moniz. Moniz instituted prefrontal lobotomy as a form of treatment for certain emotional disorders, especially aggressive conduct disorders, in human psychiatry. The behavioral consequence of ablation studies largely depended on the anatomical region of the prefrontal cortex that was removed. The prefrontal cortex in mammals can be di-

vided into a medial frontal cortex, comprising the orbital and inferior convexity, and a lateral frontal cortex, comprising the dorsal convexity. Lesions both of the inferomedial frontal cortex and of the dorsolateral cortex are associated with a possible increase in aggressive conflicts, albeit based on totally different underlying cognitive mechanisms.

Biochemical substrates in aggression and impulsivity

The influence of the neurotransmitters serotonine, norepinephrine and dopamine, and of hormones (particularly the sex hormones) is demonstrated in aggressive behavior in animals. In biological psychiatry, most research on impulsivity has been carried out with probes investigating the serotonin system. Research on the impact of the serotonin system on behavior can be done both by indirect and by direct studies. *Indirect studies* involve (1) the measurement of serotonin and its principal metabolite 5-HIAA in plasma and cerebrospinal fluid (CSF), and (2) the manipulation of the serotonergic system by interfering with the synthesis, by quantification of the serotonin receptors on blood platelets and by influencing the serotonergic system with pharmacological interventions. *Direct studies* involve (1) brain measurements of serotonin and its metabolites via *in vivo* microdialysis studies, and (2) the assessment of receptor density and function with *postmortem* autoradiographic and immunohistochemical studies and with functional brain imaging studies *in vivo*.

Most studies point to a deficient serotonergic system. However, the research results are limited to a significant extent by the quick postmortem alterations of brain receptors, by the unproven correlation between peripheral and central nervous measurements, and by the imprecise targeting of one type of neurotransmitter or receptor. Besides methodological problems, however, another significant shortcoming of the majority of these techniques lies in the absence of any topographical localization of the biochemical deficit.

Functional neuro-imagingtechniques

Both single photon emission computed tomography (SPECT) and positron emission tomography (PET) can be used for *in vivo* imaging of the brain utilizing specific radioligands. These techniques offer access to the "living" brain, thus creating the possibility of investigating the pathophysiology of behavioral disorders such as aggression and impulsivity, of investigating the effects of environmental stimuli, and of evaluating the effects of pharmacological interventions. Another important advantage is that the interaction of different neurotransmitter systems can be investigated with so-called challenging experiments, where the altered binding properties of a specific radioligand to receptors of a particular neurotransmitter system may be explored by manipulating another neurotransmitter system. Within the context of the investigation of impulsivity and aggression, functional neuroimaging studies with SPECT or PET, using specific radiolabeled tracers to assess brain perfusion or metabolism, demonstrated prefrontal hypoperfusion or hypometabolism in the prefrontal and temporal cortex in violent humans.

Recently, the feasibility of the serotonin-2A receptor radioligand ^{123}I-5I-R91150 in the estimation of the 5-HT2A canine brain receptor index was demonstrated. In the pilot study described below, this specific radioligand was used to investigate the 5-HT2A receptor binding index in impulsive, aggressive dogs.

METHODOLOGY AND RESULTS

In a pilot study involving four impulsive, aggressive dogs, which were compared with age-matched non-impulsive individuals, a significant difference was found in 6 out of the 10 brain regions examined (the frontal, temporal, parietal and occipital cortical region, the subcortical area and the cerebellum (used as a reference region)). The demographic and behavioral data of these dogs are displayed in Table 1. These biting incidents were unpredictable and without the typical preceding warning ritual signals and, moreover, the severity of each attack was out of proportion to the provoking stimuli. All four dogs were referred after thorough examination by clinicians who were experienced in the examination and therapy of behavioral disorders in dogs. The imaging examination was performed with the specific radioligand ^{123}I-5-I-R91150. The selectivity of this ligand for 5-HT2A receptors with regard to other neurotransmitter receptors such as other 5-HT receptors, including 5-HT2C and 5-HT1A, dopamine receptors, adrenergic receptors and histamine receptors is at least a factor of 50. The examination was performed using a triple head gamma camera, dedicated for brain investigations. The Mann Whitney U test was used to compare differences in regional binding index between the impulsive and the normal dogs. The level of significance was set at $p < 0.05$.

Table 1. Demographical and behavioural data
GR = Golden Retriever; JR = Jack Russel; LR = Labrador Retriever; R = Rotweiler

Breed	Age	Sex	Victims	Bites without warning	Severity of bites	Predictability
GR	12 m	M	Owner Family Strangers	> 5 bite incidents	Superficial wounding	No prodomal warning signs
R	48 m	M	Owner Family Strangers	> 5 bite incidents	Perforating bites	No prodomal warning signs
LR	18 m	M	Owner Family Strangers	> 5 bite incidents	Superficial wounding	No prodomal warning signs
JR	20 m	M	Owner Family Strangers	> 5 bite incidents	Severe wounding	No prodomal warning signs

The binding index was significantly increased in the frontal, temporal and occipital regions. The binding in the mean cortical regions was also significantly higher. There was no difference present between the two groups in the subcortical regions.

DISCUSSION

This pilot study demonstrates a higher serotonin-2A binding index in the frontal, temporal and occipital cortexes. The involvement of serotonin dysfunction in impulsivity which is established in this pilot study is in keeping with the literature. As previously mentioned, up to the present time, the *in vivo* studies demonstrating the involvement of the serotonergic system in impulsivity have consisted mainly of indirect studies. First, in research on the feasibility of the 5-HIAA-CSF probe, a significant correlation between levels of 5-HIAA in the cortex and in the cerebrospinal fluid has been demonstrated, and it has also been demonstrated that the level of 5-HIAA in CSF reflects presynaptic serotonergic activity in the brain. Numerous studies have applied this paradigm to the study of impulsivity and aggression in humans, mammals and rodents. In research in humans, the reduction of 5-HIAA levels in CSF in those who attempt violent suicide, in patients with increased lifetime aggressive incidents and in subjects committing impulsive offences is one of the most established and replicated findings in biological psychiatry. Measurements of 5-HIAA concentration in the cerebrospinal fluid of non-human primates were inversely correlated with escalated aggression and wounds requiring medical intervention or with excessive mortality due to aggressive interactions and risk taking behavior: leaving the flock at a young, immature age, performing leaps in trees at dangerous heights and over risky long distances. In dogs, a study showed that CSF 5-HIAA was lower in the aggressive group as compared to normal subjects. A very interesting finding in this report was that the levels of 5-HIAA were significantly lower in a subgroup of dogs exhibiting impulsive aggression compared to dogs that warned before biting. This was an indication that an impaired serotonergic turnover was especially related to impulsivity and, to a lesser extent, to aggression.

Secondly, and also indirect in nature, experimental challenges that interfered negatively with the synthesis of serotonin were carried out. In human studies, dietary tryptophan depletion led to behavioral inhibition in aggressive patients or to impulsivity in individuals with a genetic vulnerability to alcohol abuse. Muricidal behavior in rats was increased by a dietary reduction of tryptophan (a serotonin precursor), by

Fig.1. Perfusion defects in the left fronto-cortical brain region (large arrows), as compared to the contralateral side (small arrows), in an aggressive human patient. These SPET images (transversal slices) are obtained with the radiopharmaceutical ethyl cysteinate dimer (ECD) labeled with 99m-technetium.

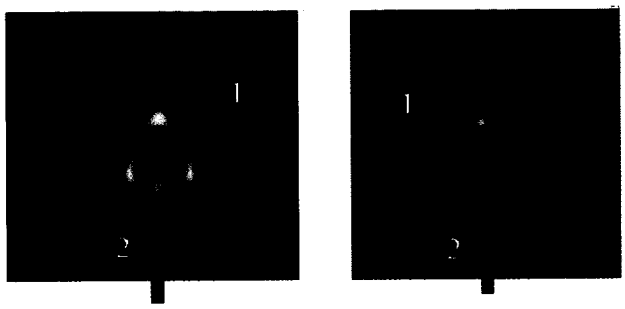

Fig. 2. The left image shows regional brain perfusion in a normal dog. The right image illustrates the distribution of the serotonine-2a receptor, visualized with the specific radioligand ^{123}I-5-I-R91150. For purposes of comparison, both transversal slices were taken at the same level in the brain.Arrow 1 marks the frontocortical area. In the right image this region shows high radioactivity as compared with the region marked with arrow 2. This activity represents binding of the radioligand with the receptor. In the cerebellar area, a region void of 5-HT2A receptors, low radioactivity is seen in the right image (arrow 2).

drugs eliciting relatively selective axonal degeneration of serotonin-containing neurons, or by blocking tryptophan hydroxylase – the rate-limiting enzymes for serotonin synthesis – with p-chlorophenylalanine (PCPA). Tryptophan-free food mixtures increased and tryptophan-rich mixtures decreased aggression in monkeys. This might imply that tryptophan-supplemented low protein diets could be used to reduce aggression in dogs.

The use of serotonergic enhancing drugs such as the selective serotonin re-uptake inhibitors and the serotonergic tricyclic anti-depressants constitutes a third significant piece of evidence in support of the role of serotonin in impulsive and aggressive behavior. In humans, the anti-aggressive effect on impulsive aggressive personality-disordered individuals has been demonstrated. In monkeys, fluoxetine-treated subjects had significantly lower scores on a social impulsivity index then did drug-free subjects. In dogs, fluoxetine was demonstrated to be useful in the management of dominance aggression in dogs. In rats, aggressive behavior was reduced by treating the subjects with citalopram. In animal studies, agonists of the serotonin-1A and serotonin-2A receptor reduced impulsivity in rats.

Concerning our finding on the serotonin-2A receptor, in human medicine a peripheral model with platelets is available to evaluate the brain serotonin-2A receptor status. These platelet studies on impulsive subjects, such as impulsive suicide attempters, demonstrated an increased platelet 5-HT2A binding. It would be of great practical interest to study the possible correlation of brain receptor occupancy with platelet receptor binding in dogs. This would, in theory, allow the screening of blood samples, thus providing a tool that may give access to a large series of normal and impulsive individuals. This pathway needs to be further elucidated, however, since a study exists that demonstrates that alterations of 5-HT2A receptors on platelets may not indicate similar changes in central 5-HT2A receptors.

In this pilot study, it is mostly cortical regions - and not subcortical regions – that seem to be involved in impulsive aggressive behavior in dogs. This finding could be partially artifactual due to the limited number of subjects and the methodological problem of adequately scanning subcortical regions because of the technical limitations of the SPECT technique. Nevertheless, there is a reasonable hypothesis that can explain the disturbed frontal cortex binding index and its link to frontal cortex related behavioral disturbances in impulsive dogs.

On the basis of theories relating to the role of frontal cortex in behavior, two major parts of the mammal brain, the orbito-frontal and the dorsolateral prefrontal cortex, may play a role in the regulation of behavior. First, regarding the orbitofrontal and medial cortex, there is evidence that at least a part of the canine's medial prefrontal cortex – the pregenual area – is, like the orbital cortex in the monkey, essential for the inhibition of inappropriate behavioral responses. For example, lesions in monkeys and humans and medial frontal lesions in dogs and cats were related to an increased number of aggressive conflicts because these subjects were found to be more easily distracted, and hence over-reactive to stimuli. The subjects suffer from the basic inability to inhibit behavioral reactions when they need to be inhibited. Secondly, lesions of the dorsolateral cortex can also add to disinhibitive behavior.

For example, large lobectomies that spare the posterior orbital tend to increase the aggressiveness of the monkey. This effect is peculiar because it occurs in conjunction with a general diminution of the communicative expressions that normally accompany aggression. There is a decrement of threats and of all those symbolic gestures and moves with which the normal monkey warns of impending aggression or asserts dominance and position in the hierarchy. The dorsolateral monkey attacks others, often without apparent motive or warning, not being guided by the customary interchange of signals. The precise neuropsychological deficits in dorsolateral animals, as in dorsolateral humans, are executive in nature. Executive functioning can be defined as the capacity to organize cognitive-specific resources to allow the development of contextually sensitive plans and flexible responses. Hence, the dorsolateral cortex can be identified as the seat of execution capacity of most other cognitive functions and motor behavior based on sensory input. Dysexecutive subjects fail to interact with the environment because of unplanned and unorganized responses, often unpredicted and hence impulsive in nature. Research in monkeys and large animals has shown that dorsolateral animals have a marked delayed-response deficit, an incapacity to use previously utilized patterns of avoidance , and a failure to integrate and recognize communicative signals. Dorsolateral deficits provoke not only behavioral deficits but also reduce learning abilities because of reduced working memory capacities. This has an impact not only on behavioral therapy strategies in human psychiatry but presumably also in veterinary medicine.

In general, further exploration of this technique makes sense, not only regarding research on the pathophysiology of this aberrant behavior, but also from a clinical point of view. This investigation can at least add to the public debate on canine aggressive behavior. Indeed, canine aggression towards humans, which is often impulsive, has a major impact on the victims, varying from superficial wounds to permanent disability and even lethal physical damage, especially in children. Besides physical injury, it also has significant effects on the psychological functioning of the attacked person, with post-traumatic stress disorder and avoidance behavior as possible consequences. Since dog bites are recognized as a public health problem, authorities are "forced" to take measures, varying from the elimination of dogs that provoke incidents to restrictions on breeding. In the absence of objective tests to provide measurable data for the purpose of evaluating and predicting canine impulsive aggression, evidence-based preventive action such as breeding restrictions and therapeutic interventions are not available, and hence, in practice, the elimination of the subjects at risk is the most logical solution in the majority of cases.

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