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Research report

Effects of acute intra-cerebral administration of the 5-HT$_{2A/C}$ receptor ligands DOI and ketanserin on impulse control in rats

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ABSTRACT

Impulsivity or diminished inhibitory control of behavior (impulse control) is a prominent feature of several neuropsychiatric diseases. Serotonin (5-HT) plays an important role in impulse control. In order to examine the role of 5-HT$_2$ receptors in a network comprising the orbitofrontal cortex (OFC) and the basolateral amygdala (BLA) in impulse control, the present study investigated effects of local infusions of the 5-HT$_2$ receptor ligands DOI [(±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride] and ketanserin on the performance of rats in the 5-choice serial reaction time task (5-CSRTT). Simultaneous bilateral infusion of the 5-HT$_{2A/C}$ receptor agonist DOI (5 μg/0.3 μl) into the OFC and the BLA significantly increased impulsive responding in the 5-CSRTT. These data suggest that both the OFC and the BLA are implicated in the mediation of DOI-induced impulsivity in the 5-CSRTT. Furthermore, these data support the notion that impulsivity caused by excessive 5-HT receptor stimulation is not mediated by just one particular brain structure, but rather by additive effects in at least two cortico-limbic structures, or perhaps by interactions of different transmitter systems within forebrain circuits.

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1. Introduction

Impulsivity and other forms of deficient impulse control frequently occur in certain neuropsychiatric diseases. However, diminished inhibitory control of behavior might also have some adaptive value and may have evolved naturally to allow individuals to adapt to uncertainty, complexity and rapidly changing environments [38]. Thus, moderate levels of impulsivity can be considered as a feature of normal behavior or a personality trait to cope with everyday life [45,16]. However, high levels of impulsivity are associated with a wide range of psychiatric disorders, including Antisocial Personality Disorder, Borderline Personality Disorder or Attention Deficit Hyperactivity Disorder [3,39]. Notably, impulsivity is not a unitary construct but rather a set of diverse and complex behavioral traits that are dissociable with respect to their neuroanatomical and neurochemical basis [17]. Common aspects of impulsivity comprise decreased inhibitory control, intolerance of delay to rewards, quick decision-making due to a lack of consideration, as well as other deficits such as poor attention and hyperactivity [13,28]. In clinical research, impulsivity has frequently been tested in humans using the continuous performance task (CPT) [30,38]. The preclinical analogue of the CPT designed for rodents is the 5-choice serial reaction time task (5-CSRTT), where animals are required to be attentive and withhold from premature responding while monitoring five apertures for brief light stimuli presented randomly therein [32]. Premature responses made in this task are considered as an operational measure of impulsivity [45].

Even though the neurobiological basis of impulsivity is not fully understood, several studies suggest an important role of the serotonin (5-hydoxytryptamine; 5-HT) systems in impulsive behavior [4,16]. The cellular effects of 5-HT are mediated via multiple receptor subtypes, classified into seven receptor families [1]. The predominant neurochemical theory of impulsivity posits that reduced 5-HT function is associated with an increase in impulsive behavior, although the potential importance for impulse control of other neurotransmitters, such as dopamine (DA) has to be considered as well [37,28]. More recent findings revealed that decreased 5-HT function enhances or reduces impulsive behavior, depending on the 5-HT receptor subtypes and the behavioral tasks used [44]. Consistent with the effects of global 5,7-DHT-lesions [41] premature responding also appears to be increased by the selective 5-HT$_{2C}$ receptor antagonist 6-chloro-5-methyl-1-[[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl]carbamyl]-indoline (SB242084) [43]. However, the 5-HT$_{2A/C}$ receptor agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride (DOI) also increased premature responding in the 5-CSRTT [20,21] and in operant paradigms of delay of reinforcement when administered systemically [18]. Furthermore, Dalley et al. [11] showed that elevated 5-HT lev-

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els in the frontal cortex have been associated with increased premature responding in the 5-CSRTT. On the other hand, treatment with the 5-HT_{2A} receptor antagonist ketanserin leads to a decrease in premature responding in the 5-CSRTT [20,21,25,39] but has no effect on impulsive responding in an operant delayed reward task when administered systemically [39] or locally into the medial prefrontal cortex [25]. Similar effects have been caused by the 5-HT_{2A} receptor antagonist (±)-2,3-dimethoxyphenyl-1-[2-4-(piperidine)-methanol] (M100907), which reduced premature responding in the 5-CSRTT as well as in an operant delayed reward task [40,43,8]. Due to the fact that different tests of impulsivity probe different cognitive processes [18] it is still unclear what generalizations towards 5-HT_2 receptor involvement can be made on the basis of measurements of impulsive behavior.

According to the possible brain sites of 5-HT action, clinical and animal experimental studies suggest that prefrontal cortical, striatal and limbic brain regions are strongly implicated in different forms of impulsivity [12,31,44]. Unfortunately, the precise mechanisms by which these brain structures and their possible interactions affect impulsivity are not well understood. Some brain areas are probably differentially involved in different forms of impulsivity [26].

Humans with OFC-damage are impaired in a number of tests of emotionality and make inadequate decisions as a result. Interestingly, the behavior of these patients resembles amygdala-lesioned subjects in certain respects. In both cases subjects are impaired in the capacity to assess and use the value of predicted outcomes to guide their actions in the *Iowa gambling task* [2], so that the patterns of behavior of these patients are described as impulsive. Likewise, OFC and BLA lesions in rats often cause similar behavioral effects on impulse control [35]. On the other hand, BLA and OFC lesions can have opposite effects in exactly the same paradigm, suggesting that the interaction of these structures is likely to be complex [6]. Overall, these findings suggest that both structures are important nodes in the cortico-limbic-striatal network regulating impulsive behavior [5,34]. In order to enhance our understanding of the involvement of forebrain 5-HT in impulsivity, the present study systematically investigated the role of 5-$HT_{2A/C}$ receptors in the OFC–BLA-network in impulse control measured in the 5-CSRTT.

2. Experimental procedures

Subjects. A total of 34 adult male Wistar rats (250–350 g) purchased from Harlan Germany (Hannover strain, Borchen, Germany) were kept in groups of four to five under controlled ambient conditions (22 °C, 12 h light/dark cycle, lights on at 7:00 a.m.). The rats received free access to tap water and were maintained on their experimental body weight by controlled feeding of 12 g standard laboratory rodent chow/rat/day (Nohrlin GmbH, Bad Salzuflen, Germany). This controlled feeding schedule continued throughout the whole testing period, keeping the animals' body weight on approximately 85% of the free feeding weight. All behavioral testing was done during the rats light cycle between 9:00 a.m. and 5:00 p.m. The experiments were performed in accordance with the NIH ethical guidelines for the care and use of laboratory animals for experiments and were approved by the local animal care committee (Senatorische Behörde, Bremen, Germany).

5-CSRTT. A detailed description of the nine-hole apparatus and procedures has been provided previously [7]. Briefly, rats were trained to spatially discriminate short light stimuli, presented randomly in one of the five apertures after a fixed delay (intertrial interval, ITI = 5 s), with a stimulus duration of 1 s. Nose poke response into the illuminated aperture during a short period of time after illumination (limited hold period, LH = 5 s) was rewarded with the delivery of a food pellet. Responses into any other aperture (error of commission) or responses made before the target stimulus occurred (premature response) just as failure to respond at all during the LH (omission) were punished with a 5 s time-out (all lights off). Additional nose poke responses made after the presentation of the stimulus in any aperture (perseverative responses) and additional responses made at the food magazine before or after food retrieval (perseverative panel pushes) were recorded although not punished. The animals did not start training on these criteria, rather it was reached in a stepwise progression where initial stimulus duration and LH were decreased continuously, while one test session lasted for 100 trials or 30 min, whatever was shorter. Animals underwent surgery when their accuracy was greater than 70% and omissions were fewer than 20% over five consecutive daily test sessions (<10% variation).

Surgery. Rats were anesthetized with chloral hydrate (360 mg/kg, Sigma–Aldrich, Steinheim, Germany) and secured in a stereotaxic frame. Bilaterally, 23 gauge stainless steel guide cannulae were implanted aiming 2 mm above the intended injection site in the OFC and BLA. The coordinates used for the final injection sites were as follows: OFC anteroposterior +3.2 mm (from bregma) mediolateral ±2.6 mm and dorsoventral −5 mm; BLA anteroposterior −2.8 mm (from bregma), mediolateral ±4.7 mm and dorsoventral −8.2 mm [27]. Anchor screws were fixed to the skull to secure all mounted material, and the guide cannulae were embedded in dental acrylic applied to the exposed skull surface. The guide cannulae were closed by removable obturator plugs of the same length before and between the experiments. After surgery animals were housed individually for two days with free access to food and tap water. After five days of recovery rats were group-housed and retrained on the 5-CSRTT until they reached pre-surgical baseline performance over five consecutive daily sessions before starting with the microinjections.

Experimental design. The parameters of the 5-CSRTT during drug testing were identical to those used in the training (stimulus duration = 1 s, ITI = 5 s, limited hold = 5 s). Due to the fact that rats should obtain a maximum of four infusions into the same brain area, we ran experiments where animals were divided into two different treatment groups. Depending on the particular treatment group, rats received combined bilateral infusions of DOI, ketanserin and saline according to a latin-square design. Subject groups were divided as follows:

Group I (n = 13): DOI into the OFC and saline into the BLA; saline into the OFC and DOI into the BLA; DOI into both the OFC and BLA; saline into both the OFC and BLA.

Group II (n = 7): ketanserin into the OFC and saline into the BLA; saline into the OFC and ketanserin into the BLA; ketanserin into both the OFC and BLA; saline into both the OFC and BLA.

The micro-infusion procedure started with one drug infusion combination after the animals showed a stable baseline performance over five consecutive test sessions (accuracy > 70%, omissions < 20%) and continued every other day, while the days between drug testing were used for normal training to re-establish the animals' baseline performance. The bilateral infusions of the drugs into the OFC and the BLA were carried out simultaneously via two double-syringe systems. These double-syringe-systems provided the accomplishment of four infusions at the same time.

Infusion procedure. Before each micro-infusion, rats were gently restrained while the obturator plugs were removed. Custom-fabricated 22 gauge injectors, connected with microliter syringes (SGE Scientific Glass Engineering, Darmstadt, Germany) via polyethylene tubes were inserted into the four guide cannulae. The injectors were left in place for 1 min before starting micro-infusions. Rate of injection was 0.1 μl/30 s, where the application of the compounds was controlled via movement of assigned bubbles within the injection tubes. The injectors were left in place for an additional minute to allow the solution to diffuse into the parenchyma and to reduce the possibility that the injected compound was drawn back when removing the injection cannulae. The injectors were then removed carefully and the obturator plugs replaced. All rats were monitored for behavioral side effects during the procedure. After microinjection (ca. 6 min) rats were immediately tested in the 5-CSRTT.

Drugs. The selective 5-$HT_{2A/C}$ receptor agonist DOI [(±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropan hydrochloride] and the selective 5-HT_{2A} receptor antagonist ketanserin were purchased from Sigma–Aldrich (Chemie GmbH, Steinheim, Germany). Both compounds were dissolved in 0.9% saline and made freshly on each treatment day. For the intra-cranial micro-infusion drugs were administered bilaterally at a dose of 5 μg/0.3 μl into the regions of interest. The drug doses used here have previously been used for microinjection studies on behavior and were reported to be effective [e.g. 36]. Due to the fact that rats should obtain a maximum of four infusions into the same brain area, we only administered a single dose.

Histology. Upon completion of the microinjection experiments, rats were anesthetized with a lethal dose of chloral hydrate and perfused transcardially with 0.1 M phosphate-buffered formaldehyde (pH 7.4). The brains were removed from the skull and immersed in a 4% formalin/30% sucrose solution for at least 24 h. To verify the appropriate location of the tips of the infusion cannulae, coronal sections of 50 μm of the OFC and BLA were cut on a freezing microtome and Nissl-stained with thionin. Locations of the injector tip positions were analyzed using a light microscope and mapped onto standardized coronal sections of a rat brain stereotaxic atlas [27].

Statistical analysis. The descriptive statistics is based on means, and variance is indicated by the standard error of the mean (±SEM). All statistical analyses were conducted using the statistical software SigmaStat (Version 2.0 for Windows). A value of $P < 0.05$ was considered to represent a significant effect. The following behavioral measures were investigated: the percentage of correct responses made (number of correct responses/total correct and incorrect responses), percentage of responses omitted (number of omissions/total number of correct, incorrect, and omitted responses), percentage of premature responses (number of premature responses/total number of correct, incorrect, and omitted responses), and the percentage of perseverative responses (number of perseverative responses/total number of correct, incorrect, and omitted responses). Within each injection group data of the mentioned measures were analyzed using repeated-measures one-way analysis of variance, followed by post hoc Tukey's t-test for pairwise comparisons.

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