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Effects of 5-HT_{1A} and 5-HT_{2A} receptor stimulation on temporal differentiation performance in the fixed-interval peak procedure

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Abstract

We examined the effects of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and 5-$HT_{2A/2C}$ receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) on performance on the fixed-interval peak procedure, and the sensitivity of these effects to 5-HT_{1A} and 5-HT_{2A} receptor antagonists (*N*-[2-(4-[2-methoxyphenyl]-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide [WAY-100635] and ketanserin). Rats were trained to press a lever for food reinforcement in 50 min sessions consisting of 32 trials in which the lever was continuously available, separated by 10 s inter-trial intervals. In 16 trials, reinforcement was delivered following the first response after 30 s had elapsed since trial onset (fixed-interval 30 s). In 16 randomly interposed (peak/probe) trials, reinforcement was omitted, and the lever remained in the operant chamber for 120 s. Response rate in probe trials was plotted against time from trial onset. Time to peak response rate (t_{peak}) and the Weber fraction were derived from modified Gaussian curves fitted to each rat's data. 8-OH-DPAT (0.05 mg kg^{-1}) reduced t_{peak} and increased the Weber fraction; the effect on t_{peak} was antagonized by WAY-100635 (0.1 mg kg^{-1}). DOI (0.25 mg kg^{-1}) also reduced t_{peak} and increased the Weber fraction; the reduction of t_{peak} was antagonized by ketanserin (2 mg kg^{-1}). Stimulation of 5-HT_{1A} and 5-HT_{2A} receptors alters temporal differentiation in qualitatively similar ways.

Keywords: Fixed-interval peak procedure; Temporal differentiation; 5-HT_{1A} receptors; 5-HT_{2A} receptors; 8-OH-DPAT; WAY-100635; DOI; Ketanserin

1. Introduction

Performance on several types of interval timing schedule is sensitive to acute treatment with drugs acting at 5-hydroxytryptamine (5-HT)$_{1A}$ and 5-HT_{2A} receptors.

The 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) has been tested in several types of timing task, including the free-operant psychophysical procedure (Stubbs, 1976) and the interval bisection task (Catania, 1970). In the free-operant psychophysical procedure (Stubbs, 1976), reinforcement is provided intermittently (usually on a variable-interval schedule) for responding on two levers, A and B; reinforcers are allocated to A in the first half, and to B in the second half, of each trial. Relative response rate on B increases as a sigmoid function of time from trial onset (see Killeen et al., 1997). 8-OH-DPAT displaced this psychometric function to the left, this being reflected in a reduction of the indifference point, T_{50}; however, the slope of the function was only minimally affected by 8-OH-DPAT (Chiang et al., 2000; Body et al., 2001, 2002b, 2004). Confirmation of the involvement of 5-HT_{1A} receptors in 8-OH-DPAT's effect was provided by the reversal of the effect by co-administration of the highly selective 5-HT_{1A} receptor antagonist *N*-[2-(4-[2-methoxyphenyl]-1-piperazinyl]-ethyl]-*N*-2-pyridinylcyclohexanecarboxamide (WAY-100635) (Body et al., 2003, 2004).

8-OH-DPAT produced a very different pattern of effect in the interval bisection task. In this schedule (Catania, 1970; Church and Deluty, 1977), the subject is first trained to respond on A after a brief presentation, and on B after a longer presentation of a stimulus, and is then tested with a range of intermediate durations. Proportional choice of B, plotted against stimulus duration, conforms to a sigmoid psychometric function similar to that seen with the free-operant psychophysical procedure (see Gibbon, 1991; Killeen et al., 1997). In this schedule, 8-OH-

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DPAT reduced the slope of the psychometric function, but did not alter T_{50} (Chiang et al., 2000).

In the discrete-trials psychophysical procedure (Body et al., 2002a), the subject is exposed to presentations of a stimulus of variable duration, following which it is able to make a single response on A or B, a response on A being reinforced after presentations shorter than a designated duration, and a response on B after presentations longer than this duration. (This schedule is similar to the interval bisection task, except that reinforcement is available on lever A for all durations shorter than the criterion and on lever B for all durations longer than the criterion, whereas in the convention interval bisection task, reinforcement is provided only following the short and long standard durations: Church and Deluty, 1977.) Again, performance conforms to a sigmoid psychometric function (Body et al., 2002a). 8-OH-DPAT's effect on the function resembled that seen with the interval bisection task: the slope was reduced, but T_{50} was not altered (Body et al., 2002a).

The effects of the 5-$HT_{2A/2C}$ receptor agonist 2,5,-dimethoxy-4-iodoamphetamine (DOI) on timing performance are similar to those of 8-OH-DPAT. DOI reduced T_{50} in the free-operant psychophysical procedure, an effect that was reversed by the 5-HT_{2A} receptor antagonist ketanserin (Body et al., 2003, 2004), but reduced the slope of the function in the discrete-trials psychophysical procedure (Asgari et al., unpublished). Quipazine, an agonist with high affinity for both 5-HT_3 and 5-HT_{2A} receptors, also reduced T_{50} in the free-operant psychophysical procedure (Body et al., 2005), and reduced the slope of the function in the discrete-trials psychophysical procedure (Asgari et al., 2005). In both cases, quipazine's effect was reversed by ketanserin, implicating 5-HT_{2A} receptors in the effects of quipazine in both types of timing schedule.

Drug-induced displacement of the psychometric timing function is often interpreted in terms of a change in the period of the hypothetical pacemaker that is widely believed to underlie interval timing performance (Meck, 1986, 1996; Gibbon et al., 1997). However, the divergent effects of the 5-HT_{1A} and 5-HT_{2A} receptor agonists on performance in different types of timing task defy a straightforward explanation in these terms, because according to classical pacemaker-based theories of timing, such as Scalar Expectancy Theory (Gibbon, 1977) and the Behavioural Theory of Timing (Killeen and Fetterman, 1988), the same pacemaker regulates timing performance on all voluntary timing tasks, and therefore it would be expected that a drug that affects pacemaker function would have at least qualitatively similar effects on performance on different types of timing schedule (see Zeiler, 1998; Grondin, 2001).

In searching for an alternative explanation for the effects of 5-HT_{1A} and 5-HT_{2A} receptor agonists on timing performance, it is appropriate to consider procedural differences that might distinguish those tasks that reveal T_{50}-reducing effects of these agonists from those that do not (Ho et al., 2002). One possible distinguishing feature is suggested by Killeen et al.'s (1997) proposal that timing schedules can be classified according to the relation between the organism's behaviour and the interval being timed. According to Killeen et al.'s (1997) taxonomy, two major classes of timing schedule are *immediate* and *retrospective* timing schedules (Killeen and Fetterman, 1988; Killeen et al., 1997). In immediate timing schedules the organism's behaviour comes under the control of time during an elapsing interval (*temporal differentiation*), whereas retrospective timing tasks require the organism to discriminate the durations of exteroceptive stimuli that have elapsed before the discriminative response is made (*temporal discrimination*). The free-operant psychophysical procedure fulfils the criteria for an immediate timing schedule, whereas the interval bisection and discrete-trials psychophysical schedules belong to the category of retrospective timing tasks. Viewed in these terms, it is possible that acute 5-HT_{1A} and 5-HT_{2A} receptor stimulation results in a reduction of T_{50} only in immediate timing tasks. If this is the case, one might expect that agonists of these receptors would displace T_{50} in other immediate timing tasks.

The experiments reported here tested this prediction by examining the effects of 8-OH-DPAT and DOI on performance on the fixed-interval peak procedure. This schedule (Catania, 1970; Roberts, 1981) is one of the most widely used schedules in studies of interval timing in animals (see Hinton and Meck, 1997; Matell and Meck, 2004). In standard fixed-interval trials, reinforcement follows the first response after a fixed interval has elapsed; in probe trials, reinforcement is omitted and responding is allowed to continue for a period several times longer than the fixed interval. Interval timing is revealed by the evolution of response rate during the course of the probe trials. Rising from a low level at the start of the trial, response rate attains a peak close to the designated time of reinforcer availability in the standard trials, and subsequently declines. The time of maximum response rate (peak time, t_{peak}) is the primary index of temporal differentiation, and has a theoretical status equivalent to that of T_{50} in the schedules described above (see Hinton and Meck, 1997; Killeen et al., 1997). Like the free-operant psychophysical procedure, the fixed-interval peak procedure belongs to the category of immediate timing schedules (Killeen et al., 1997). However the two schedules differ in one important respect. In the former schedule, timing is measured from proportional choice between two concurrently available operanda, whereas the latter is a single-operandum schedule. Thus, while effects of drugs on T_{50} might be influenced by alterations of the propensity to switch from one operandum to the other (see Chiang et al., 1998), effects of drugs on t_{peak} cannot readily be accounted for by such a mechanism.

2. Methods

The experiments were carried out in accordance with UK Home Office regulations governing experiments on living animals.

2.1. Subjects

Thirty female Wistar rats aged approximately 4 months and weighing 250–290 g at the start of the experiment were used. Twelve rats were used for the first treatment series and 18 for the second series (see below, *Drug treatment*). The rats were housed individually under a constant cycle of 12 h light and 12 h