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Serotonergic functions in arousal and motor activity

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Abstract

Changes in motor activity have long been used to characterize the effects of serotonergic manipulations. The prevailing view has been that serotonin typically inhibits motor output, often in reciprocity with catecholaminergic systems. Recent findings, however, indicate that the release of presynaptic serotonin by indirect agonists leads to a profound locomotor activation. Studies were performed in a behavioral pattern monitor (BPM). The BPM is an automated holeboard/activity apparatus measuring 30.5 × 61 cm, that allows detailed sequential analyses of both locomotor and investigatory behaviors. When tested under comparable conditions, direct agonists at both 5-HT_1 and 5-HT_2 receptors decrease locomotor activity in rats. With hallucinogenic 5-HT_2 agonists, this effect is dependent upon the novelty of the test environment, indicating that these compounds increase the responsiveness of the animal to the threatening aspects of the novel environment. Indirect serotonin agonists, however, increase locomotor activity and decrease investigation of discrete stimuli in the environment. The activating effects of indirect agonists such as 3,4-methylenedioxy-methamphetamine (MDMA), *para*-chloroamphetamine (PCA), or α-ethyltryptamine are dependent upon the release of serotonin from presynaptic terminals and are mimicked by direct agonists at 5-HT_{1B} receptors. Both behavioral analyses and studies with synthesis inhibitors and receptor antagonists clearly distinguish the MDMA-induced hyperactivity from that induced by amphetamine-like releasers of dopamine. Further supporting the relevance of 5-HT_{1B} receptors to the activating effects of serotonin-releasing agents, MDMA exhibits reciprocal cross-tolerance with the 5-HT_{1B} agonist RU 24969, but not with either 5-HT_{1A} or 5-HT_2 agonists or amphetamine. Thus, studies of locomotor and investigatory responses can be used to demonstrate and differentiate the effects of direct agonists at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors as well as indirect serotonin agonists. The fact that the predominant effect of serotonin releasers is locomotor activation, apparently mediated via post-synaptic 5-HT_{1B} receptors, suggests that some endogenous serotonergic systems may normally activate rather than suppress motor output.

Keywords: Serotonin; 3,4-Methylenedioxymethamphetamine (MDMA); Locomotor; Serotonin release; Fenfluramine

1. Introduction

Historically, central serotonergic systems have been seen as having primarily inhibitory effects on motor behavior. Such generalizations have persisted despite the accumulation of considerable evidence to the contrary. First, there is overwhelming evidence that the multiple serotonergic pathways in the brain subserve different functional influences [11,23,28]. Second, although the idea that serotonin inhibits motor activity originated with the observation that animals were hyperactive after lesions of the median raphe nucleus [15,23,28], selective neurotoxin lesions that produce equivalent forebrain serotonin depletions fail to produce hyperactivity [16,20,27,28]. Furthermore, selective neurotoxin-induced depletions of serotonin alter qualitative features of the response to amphetamine rather than changing the magnitude of the amphetamine response [10,27]. Similarly, depletion of serotonin with *para*-chlorophenylalanine (PCPA) either increases [9] or decreases behavioral activity [3], depending upon environmental and experiential factors. Third, there is a positive rather than negative correlation between raphe firing rates and arousal both in short-term studies [40,42] and across the sleep–wakefulness dimension [21]. Fourth, 5-HT_2 agonist actions rather than inhibition of serotonergic activity have been accepted as being responsible for the perceptual stimulation produced by hallucinogens [8,22]. Thus, the activation of serotonin systems is associated with increases in sensory and cognitive arousal. Fifth, it has become clear that antagonists at dopamine and serotonin receptors have similar effects in the treatment of schizophrenic patients.

Several attempts to assess the influences of central serotonergic systems on motoric arousal have relied on

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the effects of administrations of direct agonists at serotonin receptors. Depending upon the receptor subtype, varying effects have been observed. Typically, low doses of 5-HT_{1A} agonists decrease and higher doses increase motor activity, although several non-pharmacological factors significantly influence these effects. By contrast, 5-HT_{1B} agonists consistently increase locomotor activity in a dose-dependent fashion [32,37]. These activating effects are attributable to post-synaptic 5-HT_{1B} receptors, since they are potentiated by neurotoxin lesions of serotonin terminals [32,33,41]. Agonists at 5-HT_2 receptors, which are typically hallucinogenic, do not appear to have direct effects on motoric activity per se, but increase the sensitivity of animals to the threatening aspects of the testing environments [13]. Thus, hallucinogens consistently decrease exploratory locomotion when rats are tested in novel, but not familiar environments [1]. The influences of agonists at other serotonin receptor subtypes have yet to be tested adequately.

The studies described here focussed on a different approach to understanding the functions of central serotonergic systems, namely the use of indirect serotonin agonists. Largely by virtue of the notoriety attendant to the widespread recreational use of drugs such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA or 'Ecstasy') and 3,4-methylenedioxy-*N*-ethylamphetamine (MDE, MDEA, or 'Eve'), the behavioral and neurochemical effects of indirect serotonin agonists have received considerable attention recently. In particular, converging evidence now indicates that the release of presynaptic serotonin induced by these drugs leads to a dramatic form of locomotor activation in rats that appears to be attributable to the actions of released serotonin on 5-HT_{1B} receptors.

2. The behavioral pattern monitor

The effects of various serotonin-releasing agents have now been compared with those of direct serotonin agonists and a variety of psychostimulant drugs using a common test paradigm based on the behavioral pattern monitor (BPM). The BPM combines the features of activity and holeboard chambers and measures individual response frequencies, durations, and sequences. The BPM chamber is a 30×60 cm box which is criss-crossed with infrared beams and contains 3 holes in the floor and 7 in the walls, each equipped with an infrared beam. A microcomputer records and stores the animal's successive holepokes, rearings, and positions in an x–y coordinate system with a resolution of 55 ms in time and 3.8 cm in space. The sequential pattern of movements, holepokes, and rearings can be displayed and analyzed statistically. In addition to monitoring both locomotor and investigatory responses, the BPM allows one to assess changes in both the geometrical and dynamical structures of motor behavior. Assessments of these spatiotemporal sequences have proven to be very useful in discriminating drug effects [14,17,18].

3. MDMA-induced changes in behavioral profiles

In rats, MDMA-like drugs produce dramatic increases in locomotor activity in the BPM [12,18]. Given that MDMA is a derivative of amphetamine, the possibility was considered that its locomotor activating effects reflected a release of dopamine rather than serotonin. Analyses of the behavioral profiles of MDMA and MDE provided the first clues that the behavioral effects of these drugs were not simply due to their weak ability to induce an amphetamine-like release of dopamine. The hyperactivity produced by MDMA and its congeners is accompanied by a profound reduction of investigatory responses. Both rearings and exploratory holepokes are almost totally suppressed by MDMA and MDE [18]. By contrast, amphetamine and other dopamine-releasing agents produce concomitant increases in locomotor movements, rearings, and holepokes [17]. Furthermore, the dose-dependent and stereoselective increases in locomotor activity produced by MDMA or MDE are accompanied by marked alterations in the spatial patterning of locomotion. Rats treated with MDMA-like drugs consistently ambulate around the perimeter of the BPM chamber in unusually straight paths [4,18,35]. These patterns of hyperactivity are readily differentiated from those produced by amphetamine-like or other psychostimulants [14].

4. Contributions of serotonin release

Because the most prominent neurochemical effect of MDMA is the ability to increase serotonin release, recent studies have evaluated the contribution of serotonin release to the behavioral profile of MDMA. Selective serotonin uptake inhibitors decrease MDMA-induced serotonin release [19,29,39] and potently antagonize MDMA-induced locomotor hyperactivity [3]. Similar antagonism of MDMA-induced hyperlocomotion was observed after a PCPA pretreatment that produced a selective depletion of brain serotonin [3]. These data thus indicated that serotonin release was necessary for the particular pattern of hyperactivity induced by MDMA in this paradigm.

The behavioral effects of other drugs that increase serotonin release provided converging evidence that serotonergic mechanisms mediate the locomotor activating effects of MDMA. For example, systemic administration of *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) produced a fluoxetine-sensitive locomotor hyperactivity with spatial and temporal organization that is identical to that produced by MDMA [4]. This observation confirmed the results of

drug-discrimination studies in which MBDB was found to substitute completely for MDMA [34] and of human psychopharmacological studies in which the primary subjective effects of MBDB were reported to be the same as those of MDMA [31]. The efficacy of MBDB is particularly important in ruling out the contribution of direct dopamine release to the primary behavioral effects of MDMA, because MBDB is virtually inactive as a dopamine-releasing agent in vitro [24]. In addition to MBDB, locomotor hyperactivity that was qualitatively similar to MDMA-induced locomotor hyperactivity was observed after the administration of other serotonin releasing agents, including PCA, MDA, and others [4,35].

In addition to the phenylalkylamine-derived serotonin releasers such as MDMA, recent attention has been drawn to a tryptamine derivative that also appears to act as an indirect serotonin agonist, namely α-ethyltryptamine (AET). This drug has now been included on the Drug Enforcement Agency's Schedule 1 list because of illicit sales as a substitute for MDMA. Although structurally dissimilar to MDMA, AET is known to induce a release of presynaptic serotonin and has recently been shown to produce increases in locomotor activity and concomitant decreases in investigatory responses in the BPM [25]. Furthermore, the dose-dependent, long-lasting, and robust locomotor activation induced by AET was found to be blocked by a fluoxetine pretreatment, indicating that it depends upon an indirect serotonin agonist effect [25]. Thus, both MDMA-like drugs related to amphetamine and a tryptamine derivative related to serotonin share an ability to release presynaptic serotonin and induce locomotor hyperactivity.

One exception to the rule that serotonin releasers increase locomotor activity is fenfluramine, which releases presynaptic serotonin [19,38] and suppresses motor activity in the rat [2,45]. However, it is clear that some of the effects of fenfluramine are independent of serotonin release [43]. Although both fenfluramine and its metabolite norfenfluramine suppress activity in the BPM [7], this effect was not antagonized by the same fluoxetine and PCPA pretreatments that prevent the locomotor-activating effects of MDMA. Thus, these data indicate that the behavioral suppression produced by fenfluramine and norfenfluramine administration resulted from non-serotonergic mechanisms.

5. Serotonin receptor involvement in activating effects of serotonin releasers

A number of studies have examined the hypothesis that specific serotonin receptor subtypes contribute to the serotonergic effects of MDMA on unconditioned motor behavior. First, the behavioral effects of indirect serotonin agonists were compared with the effects of direct serotonin agonists that have some subtype specificity. The results of several dose–response studies indicate that neither 5-HT_{1A} nor 5-HT_2 agonists produce a comparable behavioral profile in the same paradigm [30,44]. However, previous studies indicate that the 5-$HT_{1A/1B}$ agonist, RU24969, increases locomotor activity in rats [32,33]. In the BPM, the behavioral effects of RU24969 resembled those of MDMA or MBDB, dose-dependently increasing locomotor activity and decreasing investigatory rearings and holepokes. In particular, the hyperactivity was characterized by repetitive spatial patterns of locomotion. Hence, the 5-$HT_{1A/1B}$ agonist RU24969 produces a behavioral activation that is similar to that of MDMA and dissimilar from the effects of 8-OH-DPAT, suggesting that 5-$HT_{1A/1B}$ receptors may be critical mediators of the activating effects of released serotonin [37]. These results suggest that MDMA and related drugs act via indirect agonist actions at 5-HT_{1B} receptors to produce behavioral activation similar to that produced by the direct agonist RU24969.

The contributions of various serotonin receptor subtypes to the effects of MDMA on rat exploration in the BPM also have been assessed by pretreating rats with serotonin receptor antagonists [6]. Both propranolol and pindolol, β-noradrenergic antagonists with affinity for 5-HT_1 receptors, antagonized S-MDMA-induced locomotor hyperactivity. Furthermore, pretreatment with (−)-propranolol but not (+)-propranolol antagonized the hyperactivity induced by S-MDMA [6]. Among non-selective serotonin antagonists, methiothepin was effective while methysergide and cyproheptadine were ineffective in antagonizing S-MDMA-induced hyperactivity. In other experimental paradigms, methiothepin has been found to be a good antagonist at 5-HT_{1B} receptors where methysergide, cyproheptadine and ritanserin were ineffective. These studies support the hypothesis that locomotor hyperactivity produced by S-MDMA in rats depends upon activation of 5-HT_1-like receptors, possibly of the 5-HT_{1B} subtype.

6. Tolerance studies

Studies of tolerance and cross-tolerance have provided additional evidence for the hypothesis that the specific participation of 5-HT_{1B} receptors contributes to the behavioral profile of MDMA [5]. Previous studies indicated that chronic treatments with MDMA, RU24969, DOI, or 8-OH-DPAT induce tolerance to their respective acute effects [5,26,33,36]. In experiments using the BPM, pretreatment of animals with the 5-HT_{1B} agonist RU24969 significantly reduced the locomotor activating effects of MDMA, while pretreatment with the 5-HT_2 agonist DOI or the 5-HT_{1A} agonist 8-OH-DPAT failed to alter the effects of MDMA [5]. In a reciprocal

experiment, animals pretreated with RS-MDMA were tested after acute administrations of saline, S-MDMA, RU24969, or d-amphetamine. A chronic RS-MDMA pretreatment not only produced tolerance to S-MDMA, but also reduced the effects of a challenge dose of RU24969 (i.e. cross-tolerance) and potentiated the effects of a d-amphetamine challenge. The fact that the development of tolerance to the activating effects of MDMA was associated with reciprocal cross-tolerance to the activating effects of RU24969 suggests that prolonged administration of MDMA stimulates and desensitizes the same neuronal circuitry that mediates the effects of RU24969. Thus, the primary behavioral effects of MDMA are antagonized by 5-HT_{1B} receptor antagonists, are mimicked by 5-HT_{1B} receptor agonists, and are attenuated after selective desensitization of 5-HT_{1B} receptors by chronic drug treatments. The weight of evidence favors the hypothesis that MDMA increases locomotor activity in rats by acting as an indirect agonist at 5-HT_{1B} receptors.

The demonstrations that the primary behavioral effects of MDMA-like drugs depend upon presynaptic serotonin release establishes these compounds as important pharmacological tools for the assessment of the functional roles of serotonergic systems. Just as the indirect agonist amphetamine has been critical to our understanding of the functions of catecholaminergic systems, indirect serotonergic agonists should provide similar information regarding serotonergic systems. To date, most of the literature regarding the behavioral influences of serotonin has been based on the effects of serotonin depletions or drugs acting directly on serotonin receptors. Compounds such as MBDB appear to be selective indirect serotonin agonists whose effects reflect the activation of the endogenous transmitter. Given the frequent mismatches between the distributions of the transmitter and the receptors, the effects of direct-acting agonists or antagonists may or may not be related to the endogenous transmitter. Relative to depleting agents or direct receptor ligands, the behavioral effects of drugs that increase serotonin release may have greater physiological relevance. Presumably, a drug that increases serotonin release exaggerates the normal function of serotonin by releasing the transmitter only from presynaptic sites where it normally is found. By acting acutely, these drugs avoid the long-term adaptations to abnormal levels of transmitters that can confound studies using depleting agents. Hence, further study of these newly identified indirect serotonin agonists should greatly increase our understanding of the functions of the various serotonergic systems.

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