Life Sciences, Vol. 48, pp. 2493-2498 Pergamon Press
Printed in the U.S.A.

MINIREVIEW

MULTIPLE POPULATIONS OF SEROTONIN RECEPTORS MAY MODULATE THE BEHAVIORAL EFFECTS OF SEROTONERGIC AGENTS

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(Received in final form April 12, 1991)

Summary

In order to establish a functional role for the various populations of serotonin (5-HT) receptors, behavioral studies have been conducted over the past decade with serotonergic agonists and antagonists. And, although there is reason to believe that certain behavioral effects may be mediated via particular populations of 5-HT receptors, evidence now suggests that some serotonin-mediated behaviors may be *modulated* by the interaction of serotonergic agents at multiple subtypes of 5-HT receptors. The generality of these effects, and the exact mechanism(s) by which they occur, have yet to be elucidated. Nevertheless, over the past year, results from several different laboratories provide a growing recognition of this novel phenomenon.

To date, at least four families of serotonin (5-HT) receptors have been identified: 5-HT1, 5-HT2, 5-HT3, 5-HT4 (for a recent review, see reference 1 and 2). The 5-HT1 receptors have been further subdivided into 5-HT1A, 5-HT1B, 5-HT1C and 5-HT1D subpopulations, and the 5-HT3 receptors are also thought to be heterogeneous. Biochemical and functional correlates have been identified for some of the 5-HT receptors, and the discovery of multiple populations of 5-HT receptors has prompted investigations to link these with various behavioral changes induced in animals by 5-HT agonists and antagonists (3) This has led to further refinement of the behavioral models and to clarification as to whether these receptors have any functional relevance. A topic of recent interest and of potential pharmacological and clinical significance is receptor/receptor interactions (i.e., the influence of one receptor system upon another). For example, receptor subtype interactions have already been reported for dopamine D1 and D2 receptors and it appears that stimulation of D1 receptors is a necessary component for the expression of the behavior induced by D2-selective agonists (see reference 4 for a recent review).

0024-3205/91 $3.00 +.00

Regulation of one receptor system by another can be termed autoreceptor regulation, heteroceptor regulation or coreceptor regulation, depending upon the neurotransmitter(s) involved and their sites of action. For example, the neurotransmitters that modulate 5-HT release from serotonergic nerve endings include 5-HT acting through 5-HT1B/1D autoreceptors, norepinephrine via noradrenergic α_2 heteroceptors, and adenosine (co-localized and co-released with 5-HT) acting via adenosine A_1 coreceptors (5). Thus, there already exists a body of evidence suggesting that interactions involving more than one type of neurotransmitter receptor can occur within the serotonergic system. However, the finding that certain behavioral effects, thought to be mediated by a particular population of 5-HT receptors, may be modulated by a different population of 5-HT receptors is relatively novel and intriguing. It should be noted that these behavioral effects may not be simple single-receptor mediated events and that such investigations are necessarily limited by virtue of the relatively non-selective nature of many of the presently available serotonergic agents. Thus, any mechanistic interpretations should be made with caution. Likewise, several different mechanisms may be responsible for the modulatory effects described below.

One of the most frequently used behavioral models of 5-HT receptor function is the head-twitch response induced in rodents by direct- or indirect-acting 5-HT agonists through activation of 5-HT2 receptors (6). This response can be modulated by other neurotransmitter systems; see Handley and Singh (6) for a brief review. Adrenergic agents do not induce the head-twitch response, but, rather, modulate the response induced by serotonergic agents. Stimulation of α_1-adrenoceptors is essential in order for the head-twitch response to occur, whereas α_2-adrenoceptor activation suppresses the response β-Adrenoceptors also modulate the head-twitch response since selective β_1- and β_2-adrenoceptor agonists potentiate the effect. Other neurotransmitter systems are also capable of modulating the effect. For example, GABA inhibits the 5-HT-induced response via stimulation of $GABA_B$ receptors and potentiates this behavior via excitation of $GABA_A$ receptors (6) Barbiturates, opiates, and hormones such as estrogens, progestrogens and ACTH are reported to inhibit the head-twitch response (6).

The non-selective 5-HT agonist 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) produces the head-twitch response in rodents; however, this response is not nearly as robust as that produced by the 5-HT2/5-HT1C agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). Indeed, co-administration of 5-OMe DMT actually reduces, in a dose-dependent manner, the head-twitch produced in mice by DOI (7). Arnt and Hyttel (8) using rats, and Heaton and Handley (9) and Darmani et al (7), using mice, have further demonstrated that the 5-HT1A-selective agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH DPAT), which by itself does not elicit the head-twitch response, is also a potent antagonist of the DOI-induced response (Table 1). Yocca et al (10) have reported similar results with 8-OH DPAT and other 5-HT1A agonists/partial agonists (e.g buspirone, gepirone, ipsapirone) using the less selective 5-HT2 agonist quipazine to induce the head-twitch response; they further reported that the 8-OH DPAT-induced attenuation is antagonized by pretreatment of the animals with the mixed 5-HT1A/β-adrenergic antagonist (±)pindolol. The non-selective (primarily 5-HT1B/5-HT1C) agonist 1-(3-trifluoromethylphenyl)piperazine (TFMPP) does not induce the head-twitch response. Arnt and Hyttel (8) have found that TFMPP partially inhibits the DOI-induced response in rats, but this effect was not observed in mice (7) The 5-HT1A/5-HT1B agonist RU 24969 was also without effect on DOI-induced head-twitch (7,13). It seems unlikely that 5-HT1B receptors are involved in modulating the head-twitch response. As might be expected, 5-HT2

antagonists (e.g. ketanserin) are capable of blocking the head-twitch induced by various serotonergic agonists; TFMPP, which exhibits appreciable affinity for 5-HT2 receptors and is probably a partial agonist with a very low efficacy, at high doses can antagonize several 5-HT2-mediated effects (11), including 5-OMe DMT-induced head-twitch (12). Thus, the partial antagonism of the DOI-induced response in rats might be attributed to the weak 5-HT2 antagonist properties of TFMPP. Overall, on the basis that the non-selective 5-HT agonist 5-OMe DMT, and that 5-HT1A-selective agonists such as 8-OH DPAT, attenuate the head-twitch response, it has been concluded that this 5-HT2-mediated effect might be under the modulatory control of 5-HT1A receptors (7-10).

An example of a 5-HT2-mediated effect that may be modulated by 5-HT1B receptors is ear-scratch stereotypy in mice. This behavioral response, alternatively termed the scratch response or scratch-reflex stereotypy, consists of the scratching of the ear or head and neck region with the hind paw (see reference 13 and literature cited therein). Ear-scratch stereotypy appears to be induced via stimulation of 5-HT2 receptors, and DOI-induced ear-scratch is antagonized by spiperone, ketanserin (13) and ritanserin (9). Simultaneous co-stimulation of 5-HT1B receptors is inhibitory to this behavioral effect (13). This conclusion was based on the findings that pretreatment with 8-OH DPAT may slightly potentiate DOI-induced ear-scratch stereotypy, whereas both TFMPP and RU 24969 potently inhibit the induced behavior. [One study reports that 1 mg/kg of 8-OH DPAT produces a non-significant 160% increase in ear-scratch stereotypy induced by 2.5 mg/kg of DOI (13), whereas another reports that the response is increased to 188% of control (9).] Non-selective indolealkylamine 5-HT agonists such as 5-OMe DMT fail to elicit ear-scratch stereotypy, but can antagonize the DOI-induced effect. Apparently, the modulation of ear-scratch stereotypy is rather sensitive to stimulation of 5-HT1B receptors. Although induction of the head-twitch response and ear-scratch stereotypy are thought to be due to stimulation of 5-HT2 receptors, it should be kept in mind that DOI (and related phenalkylamines such as DOM and DOB) also possesses high affinity for 5-HT1C receptors (14). Since both behaviors are reported to be inhibited with similar potency by spiperone and ketanserin, it seems likely that are both 5-HT2-mediated events. However, complete clarification of the mechanisms for these behavioral phenomena awaits the development of 5-HT1C-selective agents.

The "serotonin syndrome" is a behavioral response induced in rodents by stimulation of 5-HT1 receptors; although, in the past, some authors have considered the head-twitch response to be a component of the serotonin syndrome, there are mechanistic distinctions that allow them to be considered as separate functional entities (see reference 3 and 15 for a review of the serotonin syndrome). Certain aspects of this syndrome, such as forepaw treading, are produced by selective (e.g. 8-OH DPAT) and non-selective (e.g. 5-OMe DMT) 5-HT1A agonists and are believed to involve a 5-HT1A mechanism (15). DOI, which lacks significant affinity for 5-HT1A receptors (14) causes a 20-fold increase in 8-OH DPAT-induced forepaw treading when both agents are administered together (8). Bill and co-workers have reported similar results (16). Interestingly, the DOI-induced enhancement of 8-OH DPAT-induced forepaw treading is not extended to the non-selective 5-HT agonist 5-OMe DMT; that is, DOI co-treatment did not increase 5-OMe DMT-induced forepaw treading (8). This may be because 5-OMe DMT has already stimulated 5-HT2 receptors and has, thus, simultaneously enhanced its own 5-HT1A effect.

The relationship between 5-HT1A receptors, 5-HT2 receptors, and the 5-HT behavioral syndrome may be complex. Pretreatment with the the 5-HT2/5-HT1C antagonist ritanserin also enhances 8-OH DPAT-induced forepaw treading in rats (17). Indeed, several different 5-HT2/5-HT1C antagonists were found to enhance the various components of the serotonin syndrome (i.e., forepaw treading, head weaving, hindlimb abduction, flat body posture) induced by 8-OH DPAT, 5-OMe DMT and gepirone (see Backus et al. (17) and references therein). It has been suggested that certain aspects of the serotonin syndrome (particularly forepaw treading and lateral headweaving) might be produced by stimulation of a population of either 5-HT1A or 5-HT2 receptors (17,18), with the former being under the inhibitory influence of a subpopulation of 5-HT2 receptors (17). Another possibility that should not be overlooked is that, particularly at high doses, 5-HT2/5-HT1C agonists and antagonists might influence release and/or reuptake of 5-HT. For example, there is some evidence ketanserin stimulates (19,20), and DOI inhibits (21), release of 5-HT by mechanisms not involving 5-HT2 receptors. To the best of our knowledge, the effect of DOI on re-uptake has not yet been investigated.

Reports of the modulation of other 5-HT-induced behaviors by serotoninergic agents can be found in the recent literature (see Table 1). From the foregoing discussion, and from the results of the studies reported in Table 1, there is evidence that functions of the various 5-HT receptors may be interdependent. Whether these modulatory effects are pre- or postsynaptic, and occur via receptor/receptor or receptor/transduction mechanisms, remains to be established. Alternatively, an apparent modulation might be complicated by production of a non-specific behavioral effect, or may involve non-specific activation (or inhibition) such as alteration by one agent of the pharmacokinetics or brain penetration of another agent. Although these factors have been examined in some investigations (17), they have not been addressed by most. On the other hand, some studies (for example, head-twitch) have involved different species of animals, different 5-HT2 agonists, and different 5-HT1A agonists, reducing somewhat the likelihood of pharmacokinetic and metabolic complications. Nevertheless, these factors should be examined more specifically in subsequent investigations.

Serotonin is believed to be involved in the regulation of various physiological functions such as appetite, sleep, body temperature, blood pressure and sexual behavior (1,2,22). Serotonin may also play a role in anxiety, depression, aggression, and certain other mental disorders (1,2,22). The modulation of one 5-HT-mediated effect by a second 5-HT mechanism may have significant ramifications with regard to drug development, and may question the wisdom of targeting research solely toward the development of site-selective serotonergic agents. For example, lower doses of a given serotonergic agent may be required to produce a specific effect if that agent simultaneously interacts at another population of 5-HT receptors to enhance this effect. Likewise, the incidence of occurrence of an undesirable side effect may be reduced or eliminated via a similar type of interaction. Indeed, due to the non-selective nature of many of the currently available serotonergic agents, some of the observed behaviors might already reflect this type of interaction; potential multiple site interactions might influence the results of various studies more than previously suspected. Thus, the concept of 5-HT receptor interactions may be worthy of further investigation both from a basic science as well as a clinical perspective.

TABLE 1. Modulation of 5-HT-induced behaviors.

Behavior	Mediated by:	Modulated by:[a]		Reference:	
1. Head-twitch response in rodents:					
	5-HT2	5-HT1A	⇓	Arnt & Hytell[8]	1989
			⇓	Darmani et al[7]	1989[b]
			⇓	Heaton & Handley[9]	1989
			⇓	Yocca et al[10]	1990
			⇓	Berendsen & Broekkamp[23]	1990
2. Forepaw treading in rats:					
	5-HT1A	5-HT2	⇑	Arnt & Hytell[8]	1989
			⇑	Bill et al[16]	1990
			⇑	Backus et al[17]	1990
			⇑	Berendsen & Broekkamp[23]	1990
	5-HT2	5-HT1C	⇓	Berendsen & Broekkamp[23]	1990
3. Ear-scratch response in mice:					
	5-HT2	5-HT1B	⇓	Darmani et al[13]	1989[b]
		5-HT1A	⇑	Heaton & Handley[9]	1989
4. Lower lip retraction in rats:					
	5-HT1A	5-HT1C	⇓	Berendsen et al[24]	1990
5. Tail-flick in rats:					
	5-HT1A	5-HT1C	⇓	Bervoets et al[25]	1990
6. Penile erection in rodents:					
	5-HT1C	5-HT1A/5-HT2	⇓	Berendsen et al[26]	1990
7. DOM-induced drug discrimination in rats:					
	5-HT2	5-HT1A	⇑	Glennon[27]	1990
8. Serotonin syndrome in rats:[c]					
	5-HT1A	5-HT2	⇑	Backus et al[17]	1990
9. Hypoactivity in mice:					
	5-HT1A	5-HT1C	⇓	Berendsen & Broekkamp[23]	1990

[a]Direction of arrow indicates that agonists for this population of receptors produce either an increase (⇑) or decrease (⇓) in the behavior. [b]Presented at the 1989 Serotonin Symposium in Maui, Hawaii; December, 1989. [c]Reflects effect of 5-HT2 antagonists; see text for further discussion.

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