Putative mechanisms of action of antidepressant drugs in affective and anxiety disorders and pain

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An enhancement of neurotransmission of serotonin (5-HT), noradrenaline, or both, underlies the antidepressant response associated with most agents presently available to treat major depression. With respect to the 5-HT system, antidepressant drugs exert immediate effects on some neuronal elements controlling overall transmission, but it is the gradual changes in neuronal responses to such treatments that are ultimately responsible for producing their therapeutic benefits. In major depression, an increase in 5-HT_{1A} transmission is thought to be a crucial determinant of the antidepressant response, whereas an enhancement of 5-HT_2 transmission in the orbitofrontal cortex may mediate the therapeutic effect of 5-HT reuptake inhibitors in obsessive–compulsive disorder (OCD). The doses of medication and the durations of treatment necessary to obtain these alterations in 5-HT transmission in various brain structures of laboratory animals are fully consistent with the conditions in the clinic necessary to attenuate symptoms in depression and OCD. It is also possible that the relief of chronic pain produced by some antidepressants may be mediated, in part, by the blockade of peripheral 5-HT_{2A} receptors. These observations emphasize the notion that the 5-HT system is endowed with different adaptive properties in various parts of the body, which, in addition to the multiplicity of 5-HT receptors, makes this chemospecific network important in many disorders.

Une amélioration de la neurotransmission de la sérotonine (5-HT), de la noradrénaline, ou des deux, sous-tend l'effet antidépresseur associé à la plupart des agents actuellement disponibles pour traiter une dépression grave. En ce qui concerne le système 5-HT, les antidépresseurs ont des effets immédiats sur certains éléments neuronaux qui contrôlent la transmission globale, mais ce sont les changements graduels des réponses neuronales à ces traitements qui finissent par produire leurs effets thérapeutiques. Dans un cas de dépression grave, on pense qu'une augmentation de la transmission de la 5-HT_{1A} constitue un déterminant crucial de l'effet antidépresseur, tandis qu'une amélioration de la transmission de la 5-HT_2 dans le cortex orbitofrontal peut entraîner l'effet thérapeutique des inhibiteurs du recaptage de la 5-HT dans des cas de trouble obsessionnel compulsif (TOC). Les doses de médicament et la durée du traitement nécessaires pour produire ces altérations de la transmission de la 5-HT dans diverses structures cérébrales d'animaux de laboratoire sont tout à fait conformes aux conditions cliniques nécessaires pour atténuer les symptômes dans les cas de dépression et de TOC. Il se peut aussi que le soulagement de la

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douleur chronique produit par certains antidépresseurs soit provoqué en partie par le blocage des récepteurs périphériques de la 5-HT_{2A}. Ces observations démontrent que le système de la 5-HT est doté de différentes caractéristiques d'adaptation dans diverses parties du corps, ce qui, conjugué à la multiplicité des récepteurs de la 5-HT, donne de l'importance à ce réseau chimiospécifique dans de nombreux troubles.

Virtually all types of drugs that have been shown to be effective in major depression exert profound effects on the function of the serotonergic (5-HT) or noradrenergic (NE) systems, or both. Although some treatments have been shown to decrease the sensitivity of certain postsynaptic 5-HT and NE receptors, it is generally believed that it is an enhancement of neurotransmission in these systems that is responsible for the improvement of the core symptoms of depression. For instance, long-term administration of tricyclic antidepressant drugs (TCAs) or of monoamine oxidase inhibitors (MAOIs) decreases the density of β-adrenoceptors and cortical 5-HT_2 receptors.[1,2] However, in depressed patients who improved by at least 50% with their antidepressant regimen, a dietary tryptophan depletion, leading to decreased 5-HT availability in the brain,[3] produced a rapid relapse of the depressive syndrome and not a further improvement.[4,5] The β-adrenergic down-regulation hypothesis is also unlikely to account, by itself, for the antidepressant response in humans for several reasons. Suffice to mention here that the prototypical antipsychotic drug chlorpromazine,[7] which is devoid of antidepressant efficacy, also down-regulates β-adrenoceptors after long-term administration.[6] This review will focus on apparent 5-HT receptor heterogeneity within classes and their differential adaptive properties to account for the therapeutic effects of antidepressant drugs in various disorders.

5-HT receptor subtypes involved in the antidepressant response

A crucial 5-HT receptor in the antidepressant response is certainly the postsynaptic 5-HT_{1A} subtype, at least in certain critical brain structures. This is based on the following lines of preclinical and clinical evidence. Given the wide variety of symptoms presented by patients suffering from major depression, the pathophysiology of this disorder has to involve perturbations of neuronal functions in several brain structures. Although experimental studies in our laboratories have examined the impact of antidepressant treatments in various cerebral structures, efforts were mainly concentrated in the hippocampus. This brain region, classically linked to learning and memory, has been shown to be atrophied in patients with major depression, perhaps to an extent that is directly proportional to the duration of the illness.[8,9] Interestingly, preclinical evidence suggests that enhanced 5-HT transmission may contribute to stimulate morphogenesis in the hippocampus.[10,11] Consequently, data gathered in that forebrain region following antidepressant treatments may be considered relevant to the therapeutics of major depression. Firstly, long-term treatment with various types of TCAs enhances the responsiveness of 5-HT_{1A} receptors on hippocampus pyramidal neurons.[12,13] This conclusion was based on the observation that the inhibitory action of 5-HT and a 5-HT_{1A} agonist applied onto these neurons through a recording electrode in anesthetized rats was greater after long-term TCA drug administration. Such a sensitization of 5-HT_{1A} receptors by TCAs has also been documented in humans, but in another brain structure: the hypothalamus.[14,15] The sensitization to 5-HT was also documented in other brain structures such as the lateral geniculate body and the amygdala, but it did not occur in the somatosensory cortex. It is noteworthy, however, that the 5-HT receptor subtype mediating the effect of 5-HT in the latter 3 structures has not been characterized. Repeated electroconvulsive shocks (ECS) also produce this sensitization to 5-HT of hippocampus pyramidal neurons, using the same electrophysiological techniques described above.[16,17] In addition, ECS up-regulates the density of cortical 5-HT_{1A} binding sites.[18] Secondly, the clinical observation that the 5-HT_{1A} agonists buspirone and gepirone have been shown to have antidepressant action,[19–21] together with their capacity to enhance 5-HT_{1A} neurotransmission in the hippocampus,[22] indicates that some subpopulation(s) of postsynaptic 5-HT_{1A} receptors exert(s) an important role in the antidepressant response (see Fig. 1).

Other classes of antidepressant drugs, such as the selective 5-HT reuptake inhibitors (SSRIs) and the MAOIs, appear to largely rely on their capacity to attenuate the function of the presynaptic 5-HT_{1A} receptors.[23] These autoreceptors located on the cell body of 5-HT neurons exert a negative feedback action on 5-HT neuronal firing.

Since firing is directly related to 5-HT release in most brain regions, it is their desensitization that will contribute to increase 5-HT transmission in projection areas.[24] It is striking that, although TCAs and ECS sensitize some postsynaptic 5-HT_{1A} receptors, they leave unaltered the sensitivity of 5-HT_{1A} autoreceptors.[25,26]

When considering together the above-mentioned apparently discrepant results from laboratory and clinical studies for a specific 5-HT receptor subtype, a confusing picture appears at first glance. However, if one does not adapt the position of extreme reductionism and considers the function of brain structures separately, a clear picture then begins to emerge. For instance, whereas SSRIs desensitize 5-HT_{1A} autoreceptors, while leaving unaltered the responsiveness of 5-HT_{1A} receptors on hippocampus pyramidal neurons, ECS sensitizes the latter postsynaptic receptors but leaves presynaptic 5-HT_{1A} autoreceptors unaltered. Therefore, both treatments enhance 5-HT_{1A} neurotransmission in the hippocampus. In other words, ECS does not modify the synaptic availability of 5-HT but renders the target receptors more sensitive to 5-HT, whereas SSRIs increase the extracellular concentration of 5-HT without decreasing the sensitivity of the postsynaptic 5-HT_{1A} receptors.[23]

These divergent alterations of 5-HT_{1A} receptor responsiveness clearly indicate that 5-HT_{1A} receptors throughout the brain are endowed with distinct pharmacological properties. Repeated ECS even desensitizes 5-HT_{1A} receptors in the hypothalamus.[26,27] Given that there is only one 5-HT_{1A} receptor that has been cloned,[28] one may therefore conclude that the expression of the receptor in different brain cells can therefore lead to distinct physiological properties. These could be attributed, for instance, to different configurations of the receptor site on the membrane, different G-protein coupling and distinct coupling to transduction mechanisms. Only with respect to the first possibility, it was reported that acute spiperone and subacute pindolol administration block

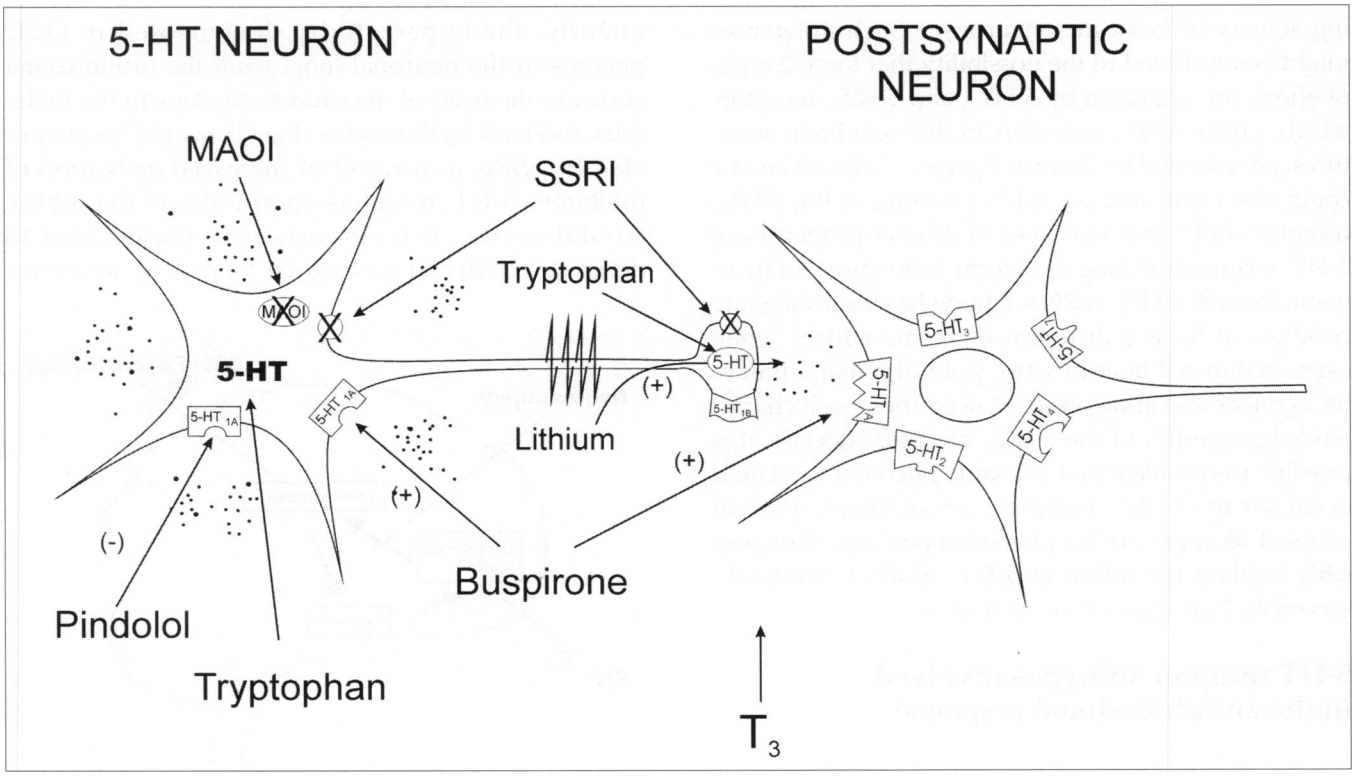

Fig. 1: The serotonin (5-HT) system depicting various elements controlling 5-HT neurotransmission and sites of action of various drugs used for the treatment of depression. Only the 5-HT receptors for which an electrophysiological role has been described are represented. The 5-HT_{1A} and 5-HT_{1B} autoreceptors on the cell body of the 5-HT neuron inhibit 5-HT neuronal firing (depicted by peaks and troughs on the axon) and release, respectively. The (+) signs indicate activation or stimulation and the (–) signs signify antagonism. The circles on the 5-HT neuron represent the reuptake transporters and the Xs indicate inhibition. The dots represent 5-HT, the concentration of which is approximately 2 times greater in and around the cell bodies of 5-HT neurons than in postsynaptic structures. MAOI = monamine oxidase inhibitor, SSRI = selective 5-HT reuptake inhibitor, T_3 = triiodothyronine.

presynaptic 5-HT_{1A} receptors on 5-HT neurons, but not postsynaptic 5-HT_{1A} receptors on pyramidal neurons in the hippocampus.[29,30] This differential capacity of pindolol to antagonize pre- and postsynaptic 5-HT_{1A} receptors has recently been documented in the human brain using positron emission tomography with the 5-HT_{1A} ligand [^{11}C]WAY-100635. Two groups of investigators have reported a preferential displacement of the radioactive ligand in the raphe area versus the forebrain using doses of pindolol similar to those used to accelerate the antidepressant action of SSRIs.[31,32] This heterogeneity of receptor subtype, even within a given subclass, therefore becomes crucial, and helpful when trying to understand and improve the therapeutics of specific illnesses.

Yet another example of such 5-HT receptor heterogeneity is the case of 5-HT_2 receptors. Long-term administration of TCAs decreases cortical density of 5-HT_2 binding sites but actually increases the responsiveness of excitatory 5-HT_2 receptors mediating the firing activity of facial motoneurons.[2,33] Such differences might be attributed to the possibility that these 2 types of effects are mediated by 5-HT_{2A} and 5-HT_{2C} receptors which, unlike 5-HT_{1A} receptors in different brain structures, are encoded by 2 distinct genes.[34,35] However, one could also claim that the mRNA editing of the 5-HT_{2C} receptor could give rise to such distinct properties of 5-HT_2 responses during long-term antidepressant treatment. Indeed, 5-HT_{2C} mRNA editing has been shown to produce at least 6 different isoforms which, when expressed in cell lines in vitro, yield different affinities for agonists and antagonists.[36] Given these well characterized properties of the 5-HT_{2C} receptor subclass, it is possible to speculate that the same phenomenon could occur for the 5-HT_{1A} receptor, yet another G-protein coupled receptor. Such a phenomenon could thus possibly explain the different 5-HT_{1A} mRNA bands observed by 2 groups of investigators.[37,38]

5-HT receptor subtypes involved in the antiobsessional response

It was postulated that an enhanced transmission at 5-HT_2 receptors in a brain structure intimately involved in controlling obsessive–compulsive symptoms could be implicated in mediating the therapeutic action of SSRIs in obsessive–compulsive disorder (OCD).[39] This was based largely on the capacity of SSRIs to enhance 5-HT release in the orbitofrontal cortex of guinea pigs after an 8-week, but not a 3-week, SSRI treatment.[40] Interestingly, 5-HT release was examined in the head of the caudate nucleus in the same animals and was found to be unaltered. The time course of this effect is fully consistent with the longer therapeutic lag of SSRIs in OCD than in depression.[41] The enhanced synaptic availability of 5-HT results from a desensitization of 5-HT_{1D} autoreceptors on 5-HT terminals, as determined by a decreased capacity of a terminal 5-HT agonist to inhibit the electrically evoked release of [^{3}H]5-HT from preloaded brain slices.[40,42] These autoreceptors, normally inhibiting 5-HT release, would then allow more 5-HT to be released in the presence of 5-HT reuptake blockade by the SSRI. Importantly, the responsiveness of neurons to 5-HT and to 5-HT_2 agonists is not attenuated in the orbitofrontal cortex, whereas the responsiveness of 5-HT_{1A} receptors is markedly attenuated.[43] It was thus presumed that 5-HT exerts its action mostly via a 5-HT_2 receptor subtype in that brain structure. Consequently, the hyperactivity documented in OCD patients in the neuronal loop, from the orbitofrontal cortex to the head of the caudate nucleus to the thalamus and back to the cortex (Fig. 2), would be attenuated by SSRIs as a result of increased activation of inhibitory 5-HT_2 receptors specifically in the orbitofrontal cortex. It is important to realize that to decrease activity in a neuronal loop, it is not neces-

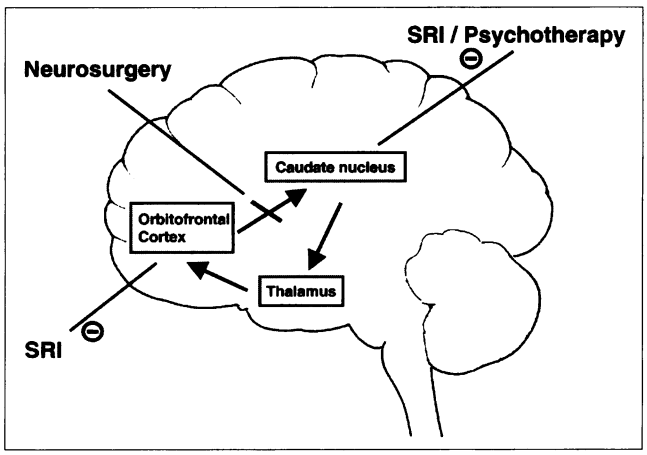

Fig. 2: The neuronal loop implicated in mediating obsessive–compulsive disorder symptoms and sites of action of different therapeutic measures. — indicates a decrease in activity and the bar between the orbitofrontal cortex and the head of the caudate nucleus, a lesion of the internal capsule where fibres pass to link the 2 structures. SRI = serotonin reuptake inhibitors.

sary to interfere with transmission at more than 1 site. What is most peculiar about this hyperactivity is that it is decreased in patients who have responded to pharmacotherapy or psychotherapy.[44] It will thus be interesting to study the effect of 5-HT_2 agonists, such as ORG-12962 in OCD, as they become available for use in humans.

5-HT receptor subtypes involved in some pain reactions

Serotonin is released from platelets when tissue is injured and plays several roles in pain. Activation of the ion-channel-coupled 5-HT_3 receptors on primary afferents produces brief pain,[45] but tachyphylaxis develops within minutes. Therefore, 5-HT_3 antagonists are not useful analgesics. Peripheral 5-HT_2 receptors are possibly important for some types of pain, acting indirectly to enhance the effects of other inflammatory mediators such as prostaglandin E2 (PGE2) or bradykinin. For example, injection of 5-HT along with PGE2 into the paws of rats produces pain that builds for 12–15 min, and this pain is blocked by local injection of nonselective 5-HT_2 antagonists, such as ketanserin.[46]

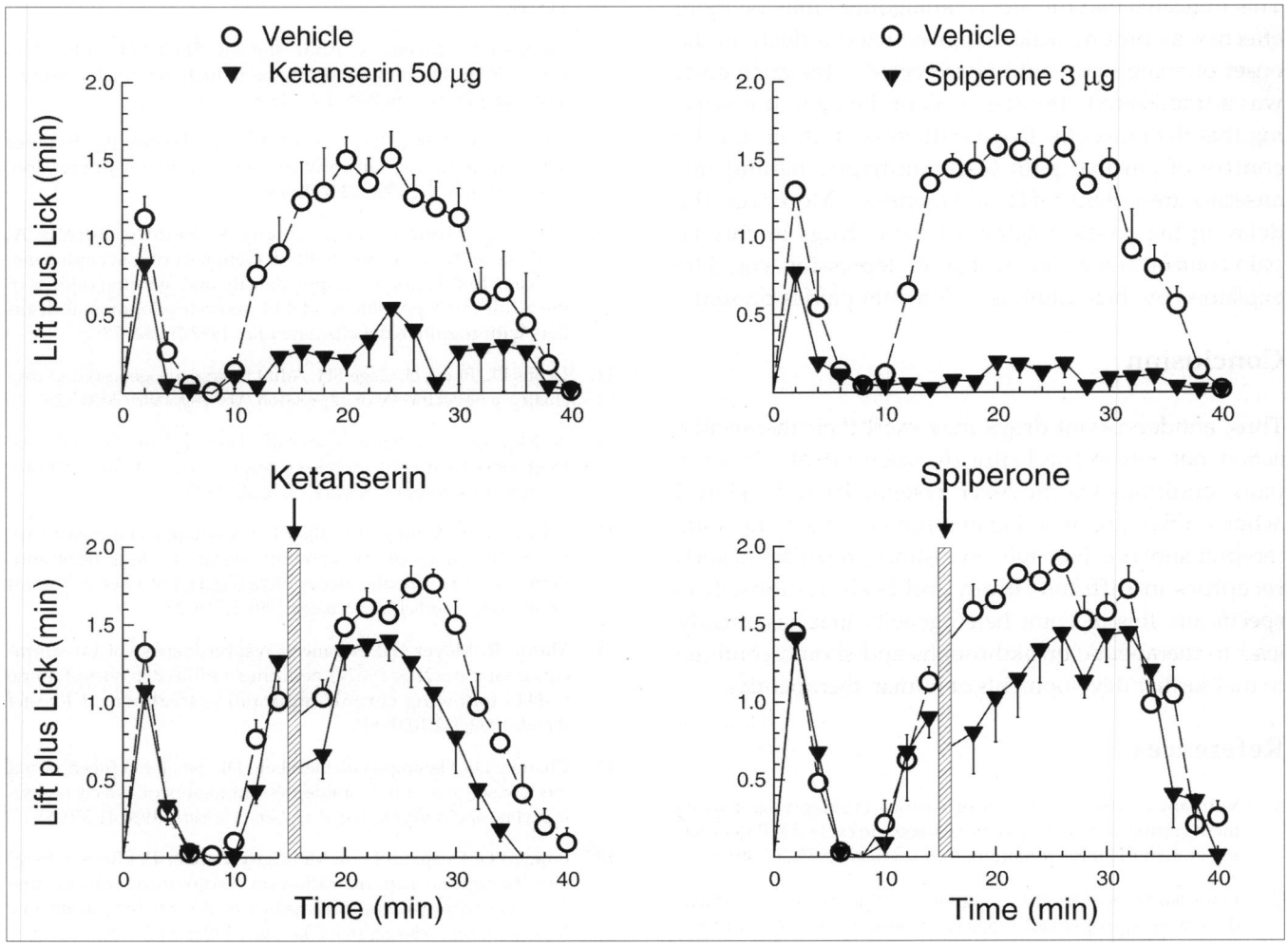

Fig. 3: Upper panels: Effects of pretreatment with 50 µg of the 5-HT_2 antagonist ketanserin, with 3 µg of the 5-HT_{2A} antagonist spiperone, or their vehicles on pain produced by 1% formalin. The antagonists injected into the paw 10 min before the formalin suppressed the second inflammatory phase of the formalin pain response, but had no effects on the first phase. Lower panels: Effects of treatment with 50 µg ketanserin or 3 µg of spiperone after the onset of the second phase of the pain response to 1% formalin. The bars represent a 2-min timeout period when injections were made. The weak effect of the antagonists is not due to kinetic factors, because opioids and adrenergic agents are equally effective, whether injected before or after the onset of the second phase.

The high efficacy of spiperone, which has 1000-fold selectivity for the 5-HT_{2A} versus the 5-HT_{2C} receptor, in this paradigm implicates the 5-HT_{2A} receptor in this phenomenon. The pain produced by injecting the non-specific irritant, formalin, into paws of rats can also be blocked by 5-HT_{2A} antagonists. Interestingly, it is the inflammatory second phase of formalin-induced pain that is blocked by 5-HT_{2A} antagonists, whereas the initial response is attenuated by 5-HT_3 antagonists (Fig. 3). With regard to the onset of action of 5-HT_{2A} antagonists, it is essential to inject them before the insult to the tissue;[47] if given after, they provide no protective action against the behavioural manifestation of pain. This indicates that the 5-HT_{2A} antagonists may be more effective as prophylactic analgesics, and a delay in the onset of analgesia would be expected if the antagonist was administered after the onset of the pain. It is striking that the most effective antidepressant drugs for the control of chronic pain (e.g., amitriptyline and mianserin) are potent 5-HT_2 antagonists.[48] Moreover, the delay in the onset of action of these drugs in chronic pain control, albeit shorter than in depression, could be explained by their administration after pain is present.

Conclusion

Thus, antidepressant drugs may exert their therapeutic action, not only in psychiatric disorders but also in some pain conditions via the 5-HT system. These beneficial actions, although involving in certain instances the same receptor subtype, may rely on distinct properties of such receptors in different brain and body regions. It is specifically this receptor heterogeneity that has already lead to therapeutic breakthroughs and should continue to fuel further developments of human therapeutics.

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