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COMMENTARY

DO ANTIDEPRESSANTS POSSESS A COMMON MECHANISM OF ACTION?

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The clinical efficacy of both the tricyclic antidepressants and the monoamine oxidase (MAO) inhibitors was discovered by chance in the 1950s. Since then, the unravelling of the mechanism(s) of action of antidepressants has been a tantalizing goal. Several factors account for this. First, depression is a major illness. It has been estimated that some 400,000 patients are treated annually in the U.S.A. and suicide is rated as the tenth greatest cause of death in that country [1]. Secondly, such information could aid in the introduction of new, more efficacious drugs possibly possessing a faster onset of action. Thirdly, such knowledge would contribute to a better understanding of the disease. It is now generally accepted that the mechanism(s) of action of antidepressants cannot be unequivocally attributed to the acute pharmacological actions of the drugs since agents possessing many of these effects lack antidepressant activity [2, 3]. Antidepressant therapy is associated with a lag phase of 1–3 weeks before the onset of a beneficial effect and it is now known that chronic antidepressant therapy is associated with a number of adaptive changes in central monoaminergic functioning [3, 4]. Drug-induced adaptive modifications can occur both pre- and postsynaptically. Regarding the former, adaptations in transmitter synthesis, storage and release occur. However, there is no common pattern of change following the chronic administration of a wide range of antidepressant therapies and the changes cannot be regarded as being primarily responsible for the therapeutic action of the antidepressant treatments [5]. Instead, the adaptive changes occurring postsynaptically during chronic antidepressant therapies are probably more pertinent to the mechanism(s) of action of the drugs. Much effort has been directed at finding a common mechanism of action for all forms of antidepressant therapy. However, on the basis of clinical phenomenology, it has been long recognized that depression does not represent a homogeneous entity [6]. A critical question to be asked is whether or not all forms of antidepressant therapy do, in fact, share a common mechanism of action. This commentary will be addressed to this issue.

Changes in the sensitivity of central beta-adrenoceptors

Radioligand binding studies have revealed that the chronic administration of tricyclic antidepressants, e.g. desipramine, imipramine, nortriptyline and amitriptyline, MAO inhibitors, e.g. pargyline, clorgyline and tranylcypromine, and repeated electroconvulsive shock therapy (ECT) is associated with a reduction in the number of beta-adrenoceptor recognition sites present in rat cortex [7–13]. However, this property does not extend to all atypical antidepressants. For example, it is generally agreed that chronic mianserin fails to alter beta-adrenoceptor binding in rat cortex [9, 13–15]. Somewhat surprisingly both cocaine [9, 16] and the specific norepinephrine (NE) uptake inhibitor nisoxetine [11, 13, 16, 17] are devoid of an effect on beta-adrenoceptor binding in rat brain. Both these agents have a short half-life in rats. However, their ineffectiveness cannot be attributed to a failure to attain and maintain a sufficiently high concentration of drug in the brain since the continuous intravenous infusion of cocaine (total dose 100 mg/kg/day) for 7 days was devoid of an effect [16]. NE uptake is also blocked by chlorpromazine [18], yet the long-term administration of the drug fails to alter rat central beta-adrenoceptor binding [9, 12]. The mechanism by which chronic tricyclics decrease beta-adrenoceptor binding awaits clarification. Incubating rat cortical slices with either isoproterenol or NE results in a reduction in beta-adrenoceptor binding sites. Reincubation in a NE-free medium or exposure to guanine nucleotides restores beta-binding. In contrast, neither of these procedures affects the decrease achieved by chronic desipramine administration. Moreover, the incubation of cortical slices obtained from rats chronically treated with desipramine in a medium containing isoproterenol results in a further decrease in the number of binding sites. Thus, it appears that the reductions elicited by chronic desipramine and by isoproterenol are mediated via separate mechanisms [19]. The fact that the long-term administration of clinically efficacious antidepressants such as mianserin fails to alter central beta-adrenoceptor binding indicates that efforts to obtain new, novel antidepressants based on the effect of chronic drug treatment on central beta-adrenoceptor binding are futile.

A key finding was the observation in 1975 by Sulser and his associates [20] that the responsiveness of the NE-stimulated adenylate cyclase system present in rat limbic forebrain slices is diminished both by repeated ECT and by the long-term administration of desipramine or iprindole. The importance of this observation is strengthened by the fact that all forms of antidepressant therapy studied to date share this effect [21]. The decreased response of the adenylate cyclase system is not due to a change in affinity since the concentration of NE needed for half-max-

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imal stimulation is unaltered. Acute therapy does not down-regulate the system. The effect is indirectly mediated since chronic desipramine is devoid of effect on NE-stimulated adenylate cyclase present in rat diaphragm, a tissue lacking sympathetic innervation [22]. Further evidence for an indirect effect is the fact that the ability of both chronically administered desipramine and iprindole to reduce the responsiveness of adenylate cyclase present in rat cortical slices is absent following locus coeruleus lesioning and at a time when the system is not supersensitive [23]. Chronic imipramine blunts the response to NE of a cell-free adenylate cyclase system obtained from rat cortex [24]. A decreased responsiveness of the beta-adrenoceptor present in the rat pineal gland has also been demonstrated following the chronic administration of either desipramine or the MAO inhibitor nialamide [25]. Potential explanations for the induced down-regulation include increased NE levels in the synaptic cleft, changes in receptor density, alterations in phosphodiesterase activity, changes in coupling factors and modifications of the properties of the cell membrane. Two of these possibilities can be discounted. The effect cannot be due to an increased availability of NE in the synaptic cleft stemming from uptake blockade since the system is down-regulated by both iprindole [20] and the specific 5-HT uptake inhibitor zimelidine [14], two drugs lacking an effect on NE uptake [26, 27]. The ability of both chronic nisoxetine [17] and mianserin [14] to down-regulate adenylate cyclase functioning without changing the number of beta-adrenoceptor binding sites indicates that both phenomena are not interdependent. It is of interest to note that chronic clonidine is associated with a supersensitive adenylate cyclase system in rat brain with no change in beta-adrenoceptor binding [28].

A down-regulation in the sensitivity of beta-adrenoceptors present in rat brain has been demonstrated electrophysiologically following chronic antidepressant administration. The responsiveness of cerebellar Purkinje cells to iontophoretic NE is blunted by long-term desipramine [29]. The sensitivity of rat cingulate cortical neurones to iontophoretic NE or GABA has been studied after the chronic administration of desipramine, chlorimipramine, maprotiline and tranylcypromine. A subsensitive response to NE, but not to GABA, was induced by all four drugs [30]. The basal firing rate of rat hippocampal neurones is increased by chronic desipramine [31]. This system has an inhibitory NE input and acute desipramine facilitates NE inhibition [32]. In contrast to these observations, it has been demonstrated in several studies that the responsiveness of rat hippocampal pyramidal cells to iontophoretically applied NE is unaltered following the chronic administration of tricyclic antidepressants, i.e. desipramine, imipramine, amitriptyline and chlorimipramine, and the atypical antidepressants iprindole and zimelidine [33–35]. NE receptors on rat hippocampal pyramidal cells exhibit the properties of a beta-adrenoceptor [36].

The observations that, under certain appropriate experimental conditions, virtually all forms of chronic antidepressant therapy down-regulate central NE-stimulated adenylate cyclase has triggered the speculation that depression may, in part, be related to a functional hyperactivity of certain NE neuronal systems. The hypersensitive receptors may serve to amplify incoming stimuli and hence cause central hyperexcitability. Thus, a hyperresponsive NE system may be an underlying cause of depression [37]. Antidepressant therapy may result in a desensitization of enhanced NE receptor functioning and hence cause a reduction in the postulated amplification mechanism that translates sensory input into physiological and behavioral events [2, 38]. It is readily apparent that this view radically differs from the original catecholamine hypothesis of depression which attributed the illness to a deficiency of the monoamine at central synapses [6]. The supersensitivity hypothesis has attractive heuristic value. However, for a number of reasons it would appear inappropriate to unequivocally view it as the sole mode of action of antidepressants. First, chronic chlorpromazine down-regulates rat brain adenylate cyclase [39], but the drug is not an antidepressant. Secondly, the increase in rat cortical c-AMP content following stimulation of the locus coeruleus was either unaltered or slightly blunted by chronic chlorimipramine or imipramine respectively [40]. This *in vivo* observation is certainly not in harmony with a down-regulated adenylate cyclase system. Thirdly, the adenylate cyclase system present in rat brain slices is an incompletely understood system. There are two receptors coupled to the system. One has the characteristics of a $beta_1$-adrenoceptor whereas the other cannot be classified as either alpha or beta [41]. Following both chronic mianserin [14] and zimelidine [14], the non-beta component is down-regulated as indicated by the ability of drug administration to decrease the response to NE but not to isoproterenol. Fourthly, should the concept that the down-regulation of beta-adrenoceptor functioning represent the sole and primary mode of action of antidepressants, it would appear logical to assume that the administration of a beta-adrenoceptor antagonist capable of crossing the blood–brain barrier would elicit a rapid remission. This is not the case and propranolol may, in fact, induce depressive episodes [42]. Fifthly, the failure of chronically administered antidepressants to change the sensitivity of rat hippocampal pyramidal cells to iontophoretic NE is not in harmony with the concept *(vide supra)*.

Changes in the sensitivity of central alpha-adrenoceptors

Electrophysiological and behavioral studies indicate that the sensitivity of central $alpha_1$-adrenoceptors is enhanced by the chronic administration of antidepressants. Long-term desipramine, imipramine, amitriptyline and iprindole are associated with an augmented response to iontophoretic NE in the rat facial motor nucleus [43]. Moreover, the response of single dorsal lateral geniculate neurones in the rat to iontophoretic NE is enhanced by chronically administered desipramine, imipramine, amitriptyline and iprindole [44]. A clonidine-induced increase in spontaneous motor activity has been observed in

rats treated chronically, but not acutely, with imipramine, amitriptyline and mianserin [45]. Furthermore, apomorphine-induced aggressive behavior in rats is enhanced by the chronic administration of desipramine, amitriptyline, iprindole and mianserin. In rats treated chronically with amitriptyline, apomorphine-induced aggressive behavior is blocked by phenoxybenzamine [46]. Clonidine-induced aggressiveness in mice is augmented by the chronic administration of a number of antidepressants [47]. Antidepressants such as amitriptyline and mianserin are potent $alpha_1$-adrenoceptor antagonists [11]. However, the possible induction of supersensitive $alpha_1$-adrenoceptors stemming from receptor blockade is not the case since effective drugs such as iprindole and zimelidine possess minimal affinity for $alpha_1$-adrenoceptors [48]. In contrast to these observations indicating an up-regulation in central $alpha_1$-adrenoceptor functioning, the chronic administration of a wide variety of antidepressant therapies is essentially devoid of an effect on rat brain $alpha_1$-adrenoceptor binding [3, 4]. Peripheral $alpha_1$-adrenoceptor sensitivity has been studied in depressives on drug therapy. Chronic desipramine does not alter ocular alpha-adrenoceptor sensitivity as assessed by mydriasis induced by the $alpha_1$-adrenoceptor agonist phenylephrine [49]. Moreover, a reduced pressor response to phenylephrine has been observed in patients on amitriptyline [50].

The view has been expressed that a drug-induced induction of subsensitive, central presynaptic $alpha_2$-adrenoceptors may play a critical role in the mechanism of action of antidepressants [51, 52]. The presence of such a phenomenon would contribute to an increased availability of NE in the synaptic cleft. This in turn could possibly account for the reduction in beta-adrenoceptor functioning cited earlier since NE hyperinnervation is associated with a decreased density of beta-adrenoceptors in rat brain [53]. The significance for the role of $alpha_2$-adrenoceptors in the mechanism(s) of action of antidepressants stems from the fact that mianserin is a receptor antagonist [54–56] and from the observations that chronically administered desipramine and imipramine induce subsensitive $alpha_2$-adrenoceptors in rat heart [57] and brain [58] respectively. Neurochemical experiments confirm the ability of both chronic desipramine and imipramine to down-regulate the sensitivity of rat brain $alpha_2$-adrenoceptors, as reflected by an attenuation of the ability of low doses of clonidine to decrease brain NE turnover [59–61]. Antagonism of the behavioral effects of clonidine is also present following the long-term administration of either desipramine [62] or imipramine [63]. The pooling of these observations strongly suggests that chronic imipramine and its demethylated congener desipramine do in fact induce subsensitive presynaptic $alpha_2$-adrenoceptors in rat brain although a somewhat different conclusion has been reached by others using a more indirect paradigm [64, 65]. The effect of other chronic forms of antidepressant therapy on rat brain $alpha_2$-adrenoceptor sensitivity is much less clear-cut. Chronic mianserin has been observed in two studies to induce supersensitive presynaptic $alpha_2$-receptors [66, 67]. This phenomenon was not observed in two other studies in which much larger doses of clonidine were employed [68, 69] and in all probability the doses of clonidine employed (>0.35 mg/kg) are in excess of those required for a selectivity of action on presynaptic $alpha_2$-adrenoceptors (<0.1 mg/kg [70, 71]). If, in fact, the induction of subsensitive central presynaptic $alpha_2$-adrenoceptors represents the fundamental mode of action of antidepressants then it would be logical to assume that the effect would be observed after the chronic administration of a wide spectrum of antidepressants possessing markedly different acute pharmacological profiles. This does not appear to be the case. In one study, the effect of the long-term administration of the following antidepressant therapies on the reduction in rat brain 3-methoxy-4-hydroxyphenylethylene glycol sulphate (MHPG-SO_4) content elicited by clonidine (25 μg/kg) was studied: amitriptyline, nortriptyline, iprindole, nisoxetine, salbutamol, trazodone, pargyline and ECT. Of all these therapies, only ECT blunted the clonidine-induced decrease in MHPG-SO_4 levels [13, 61]. The effectiveness of chronic ECT is in accord with the data of others [72]. Others have observed that the chronic administration of desipramine, but not amitriptyline or iprindole, blocks the clonidine-induced inhibition of the acoustic startle reflex in rats [73]. These observations are in harmony with the neurochemical data cited earlier. Behavioral effects of clonidine in rats have been observed to be attenuated by the long-term administration of clorgyline [74] and salbutamol [75]. Finally, the responsiveness of $alpha_2$-adrenoceptors present on rat locus coeruleus neurones is unaltered by chronically administered iprindole or chlorimipramine [76]. Viewing these observations collectively indicates that the therapeutic effectiveness of antidepressant drugs cannot be attributed to changes in the sensitivity of central $alpha_2$-adrenoceptors.

Attempts to correlate antidepressant-induced changes in central $alpha_2$-adrenoceptor sensitivity with alterations in the characteristics of central $alpha_2$-adrenoceptor binding sites have met with little success. Long-term tricyclic antidepressant administration has been observed to increase [15], decrease [77, 78] and leave unaltered [13, 79] rat brain $alpha_2$-adrenoceptor binding. A major problem with this approach resides in the precise anatomical location of the binding site. Evidence suggests a postsynaptic location [80, 81]. Platelet $alpha_2$-adrenoceptor binding has been measured in depressives. Again, the results are contradictory. The number of binding sites has been reported to be reduced [82], normal [83] and elevated [84, 85]. In one study, it has been observed that chronically administered imipramine, amitriptyline and nortriptyline decrease the number of $alpha_2$-adrenoceptor binding sites on platelets of depressives [85]. The sensitivity of central $alpha_2$-adrenoceptors has been assessed in depressives by determining certain responses to clonidine. The ability of clonidine to lower both plasma MHPG levels and blood pressure is the same in drug-free depressives and normal persons [86, 87]. However, both plasma MHPG and blood pressure responses to clonidine are attenuated by chronic desipramine [88, 89]. Chronically administered clorgyline also

blunts the hypotensive response of depressives to clonidine [90]. These observations can be interpreted as being indicative of the presence of subsensitive central presynaptic alpha$_2$-adrenoceptors.

Changes in the sensitivity of central dopaminergic (DA) receptors

Apomorphine-induced stereotypes in rats are unaltered by chronic tricyclic antidepressant administration [45, 91]. This suggests an unaltered sensitivity of striatal postsynaptic DA receptors. In contrast, the chronic administration of desipramine to rats is associated with supersensitive postsynaptic DA receptors in the mesolimbic system [91]. Repeated ECT results in postsynaptic DA receptor supersensitivity [92], but this is dependent upon the presence of intact NE neurones [93]. The induction of subsensitive presynaptic DA receptors by chronic antidepressant therapies has been observed in some [94, 95] but not in other [91, 96] studies. The presence of subsensitive presynaptic DA receptors would be expected to modify central DA turnover but this is unaltered by the chronic administration of a variety of antidepressants [5]. In an intriguing series of experiments Antelman and Chiodo [97] have demonstrated that repeated treatment with imipramine, amitriptyline, iprindole and ECT induces a progressive subsensitivity of soma-dendritic DA autoreceptors present within the zona compacta of the substantia nigra. The induction of receptor subsensitivity is dependent on the passage of time rather than on repeated daily treatments and it has been provocatively proposed that daily antidepressant therapy may be unnecessary for therapeutic efficacy [97]. In general, rat striatal DA binding is unaltered by repeated antidepressant therapies [3, 4].

Changes in the sensitivity of central serotoninergic (5-HT) receptors

As in the case of alpha$_1$-adrenoceptors, both behavioral and electrophysiological studies point to an up-regulation in the sensitivity of central 5-HT receptors following chronic antidepressant therapies. Chronic amitriptyline enhances the behavioral response of rats to 5-HTP [98] and mice [99] to the 5-HT agonist 5-methoxy-*N,N*-dimethyltryptamine. Paradoxically, the long-term administration of mianserin blunts the 5-methoxy-*N,N*-dimethyltryptamine-induced behavioral response in mice [100] and enhances the response of rats to 5-HTP [98]. The ability of acutely administered 5-HT uptake inhibitors such as fluoxetine [101] and zimelidine [102] to augment 5-HT-mediated behavioral responses is absent following their chronic administration. Repeated ECT results in supersensitive postsynaptic 5-HT receptors [92]. However, this phenomenon is absent following the prior depletion of brain NE [93]. Whilst these behavioral observations suggest an induced up-regulation in receptor sensitivity results should be treated with some reservation for two main reasons. First, most 5-HT-mediated behavioral responses are of brain stem and spinal origin [103] and it is highly improbable that these brain regions represent the primary site of action of antidepressants. Secondly, antidepressants such as mianserin and amitriptyline are potent 5-HT receptor antagonists (*vide infra*) and the possibility of receptor supersensitivity stemming from this property of the drugs cannot be excluded. Electrophysiological studies have revealed the existence of at least three types of central 5-HT receptors. One type consists of postsynaptic receptors which are inhibitory. The sensitivity of this type of receptor present in rat hippocampal, ventral lateral geniculate and amygdaloid neurones to iontophoretic 5-HT, but not NE or GABA, is enhanced by chronically administered tricyclic antidepressants [33–35]. However, this property does not extend to all antidepressants since chronic zimelidine fails to alter the sensitivity of rat hippocampal pyramidal neurones to iontophoretic 5-HT [35]. Moreover, the response may be regional since the responsiveness of rat cortical neurones to iontophoretic 5-HT is unchanged by chronic desipramine and chlorimipramine. In contrast, sensitivity is increased by chronic administration of the MAO type A inhibitor clorgyline [104]. The second type of 5-HT receptor is modulatory in nature and increases the electrical excitability of postsynaptic neurones. Chronically administered tricyclics and iprindole are associated with an augmentation of the excitatory facilitatory action of 5-HT in the rat facial motor nucleus [43]. The third type of 5-HT receptor controls the generation of action potentials in the perikarya and is located on, or near, the cell body. The responsiveness of this type of receptor in the rat dorsal raphe is unchanged by the chronic administration of both atypical and tricyclic antidepressants [35, 105, 106]. The heterogeneity of central postsynaptic 5-HT receptors has also been demonstrated by means of radioligand binding techniques. Two types of binding sites have been recognized and are termed 5-HT$_1$ and 5-HT$_2$ [107]. In general, antidepressants possess a greater affinity for 5-HT$_2$ as opposed to 5-HT$_1$ binding sites [12]. The antagonist activity of antidepressants such as amitriptyline and mianserin at central 5-HT receptors has been demonstrated *in vivo* [108, 109]. In most studies, rat brain 5-HT$_1$ binding has been observed to be unchanged by the chronic administration of both atypical and tricyclic antidepressants and by repeated ECT [10, 12, 100, 110, 111]. In contrast, chronically administered MAO type A inhibitors are associated with a reduction in the number of rat cortical 5-HT$_1$ binding sites and this effect is dependent upon the presence of unaltered brain levels of 5-HT [111]. In contrast to their lack of effect on central 5-HT$_1$ binding, chronically administered antidepressants down-regulate the number of 5-HT$_2$ recognition sites present in rat brain. This is a property common to tricyclic antidepressants, atypical antidepressants and MAO inhibitors [10, 12, 112]. However, repeated ECT is associated with an increased number of recognition sites [10, 113].

Changes in the sensitivity of other central receptors

Generally, receptor systems, other than the above, are resistant to challenge following long-term antidepressant therapy. The number of rat brain muscarinic sites is unaltered by repeated ECT [10] and by the chronic administration of a variety of antidepressant drugs [11, 12]. The effect of desipramine and amitriptyline on the histamine-induced stimu-

lation of c-AMP production in guinea pig cortical slices is not modified by the chronic administration of either drug [114]. Tricyclic antidepressants are potent antagonists at central muscarinic and histaminic binding sites and it is currently believed that such actions contribute more to the side effects of the drugs rather than to their mechanism of action [3, 4]. Of interest, is the observation that rat cortical opiate binding is decreased by chronic desipramine [115]. Other forms of antidepressant therapy remain to be studied.

Concluding remarks

A major limitation in attempting to comprehend the mechanism(s) of action of antidepressant therapies is the complete lack of appropriate models for monitoring central neurotransmitter functioning in humans. To circumvent this problem, one is forced to resort to indirect strategies such as either determining alterations in the sensitivity of peripheral receptors or using a neuroendocrinological approach. Neither is entirely satisfactory and pharmacological studies employing animals play an important role in attempting to understand how antidepressants work. A major goal has been, and is, the quest for a common mechanism of action. To unequivocally demonstrate this, it is essential that the proposed mechanism of action is common to the gamut of established therapies, i.e. tricyclics, atypical antidepressants, MAO inhibitors and ECT. In addition, other psychotropic drugs should lack activity. In many instances, a tricyclic, usually desipramine, is studied and the findings are extrapolated to all other forms of antidepressant therapy. The limitations of this approach are apparent. For example, convincing evidence is available to indicate that chronic desipramine is associated with the induction of subsensitive central presynaptic alpha$_2$-adrenoceptors in both man and rodents. However, evidence from neurochemical, behavioral and electrophysiological studies reveals that this property is not possessed by all forms of antidepressant therapies. Hence, it cannot be concluded that such an action accounts for the primary mechanism of action of antidepressants. The view has been expressed [4] that the therapeutic efficacy of antidepressants may be related to their ability to induce supersensitive central alpha$_1$- and serotoninergic receptors. This may be true for some forms of antidepressant therapy but is certainly not true for all. The inability of chronic zimelidine to up-regulate the sensitivity of central 5-HT receptors indicates that this effect is not a prerequisite for an antidepressant effect. Moreover, not all forms of antidepressant therapy have been studied. The adaptive change possessing the strongest evidence for a common mechanism of action is the induced down-regulation in beta-adrenoceptor functioning observed in rat brain slices. This phenomenon is observed after the chronic administration of tricyclics, atypical antidepressants, MAO inhibitors and ECT. However, a false positive exists, namely chlorpromazine. In addition, the reconciliation of a number of facts with the concept is difficult (*vide supra*). The concept that all forms of antidepressant therapy possess a common mechanism of action is of heuristic value. However, it may represent an erroneous strategy since depression is not a homogeneous entity as indicated by both diagnostic [6] and biochemical [116] criteria. Drugs do not have to possess a common mechanism of action in order to achieve the same final result. As an example, blood pressure can be lowered by drugs which possess vastly dissimilar modes of action, e.g. beta-adrenoceptor antagonists, central alpha$_2$-adrenoceptor agonists, agents interfering with peripheral sympathetic functioning, angiotensin converting enzyme inhibitors and calcium slow channel blockers. Complex interconnections exist among central putative neurotransmitter and modulatory systems. The functioning of one monoaminergic system can be modified by changes in another system. For example, the administration of a 5-HT reuptake inhibitor potentiates the ability of haloperidol to block rat striatal DA receptors [117, 118]. Moreover, the classical view that each neurone produces, stores and releases only one neurotransmitter is no longer tenable as neuropeptides coexist in the same neurone with a classical neurotransmitter [119]. In light of the complexity of the brain, the possibility warrants consideration that not only do multiple intervention sites into the central neuronal circuitry exist but also that chronic antidepressant therapies possess different intervention sites. Hence, while the end result downstream may be the same, i.e. clinical efficacy, the initial interaction in the chain of multiple steps leading to this goal may not be identical for all forms of antidepressant therapy. Evidence in favour of multiple intervention sites is our current inability to unequivocally attribute a common mechanism of action to all forms of antidepressant therapy.

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