Drugs of the Future 1998, 23(1): 9-16

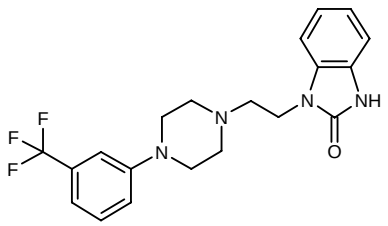
Flibanserin

Prop INN

Antidepressant
5-HT$_{1A}$ Receptor Agonist
5-HT$_2$ Receptor Antagonist

BIMT-17

1,3-Dihydro-1-[2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]-2*H*-benzimidazol-2-one



$C_{20}H_{21}F_3N_4O$ Mol wt: 390.41

CAS: 167933-07-5
CAS: 147359-76-0 (as monohydrochloride)

EN: 197146

Synthesis

Flibanserin may be prepared by reacting 1-(phenylvinyl)-2,3-dihydro-1*H*-benzimidazol-2-one (I) with 1,2-dichloroethane (II) in the presence of NaH in warm dimethylformamide. The resulting 1-(2-chloroethyl)-2,3-dihydro-1*H*-benzimidazol-one (III) is in turn coupled with commercially available *m*-trifluoromethylphenylpiperazine hydrochloride (IV) in the presence of sodium carbonate and catalytic potassium iodide in refluxing ethanol. The crude flibanserin hydrochloride (V) is then dissolved in aqueous ethanol and the pure base is precipitated upon addition of sodium hydroxide (1). Scheme 1.

Introduction

One of the still unmet medical needs in the treatment of depression is the availability of antidepressants with a rapid onset of action. Current antidepressants exert an acute effect at the presynaptic level. In general, almost all block the uptake of monoamines or inhibit the activity of the enzyme monoamine oxidase, more or less selectively. Consequently, much of the scientific literature deals with understanding the pharmacology of these presynaptic mechanisms. However, when different types of antidepressants are used, the therapeutic effects and onset times are the same for all of them, with only the side effects being different.

The therapeutic effect of the current antidepressants is achieved only after repeated administration. There is general agreement that the net effect of the antidepressants is to increase monoamine concentrations in the synaptic cleft and, consequently, to induce changes in those receptors upon which a particular monoamine acts. These phenomena need time for induction. Recently, a new potential therapeutic combination has been proposed in which a serotonin (5-HT) uptake blocker is administered together with pindolol, an antagonist at the presynaptic dendrosomatic 5-HT$_{1A}$ receptor (2, 3). This combination allows achievement of an increased 5-HT synaptic concentration in the cortex within a shorter period of time. Despite the many lines of evidence showing that postsynaptic mechanisms seem to be responsible for the therapeutic effect of antidepressants, many studies still deal with the presynaptic mechanisms and only a few concentrate on the postsynaptic mechanisms. Therefore, the problem is: does any drug act at postsynaptic receptors (mimicking the effects exerted by long-term antidepressant treatment), thus avoiding the delay due to adaptation of pre/postsynaptic mechanisms?

Of the three monoamine receptors, the postsynaptic stimulation of central β_1-noradrenergic receptors or dopaminergic (which subtype is so far unclear) receptors has been claimed to be important for the therapeutic action. However, it is very difficult to exploit these mechanisms in humans, due to predictably strong side effects. Postsynaptic serotonin 5-HT$_{1A}$ and 5-HT$_2$ receptor subtypes in the cortex have also been implicated in the mechanism of action of antidepressants (4). These receptors are more easily approached pharmacologically, due to the lower incidence of side effects associated with them. It has been suggested that repeated administration of antidepressants may enhance 5-HT$_{1A}$ receptor sensitivity, and it has been shown that such treatment induces a downregulation of 5-HT$_2$ receptors in the cortex (4).

In the 5-HT field, it is mandatory to distinguish between pre- and postsynaptic receptors, and between

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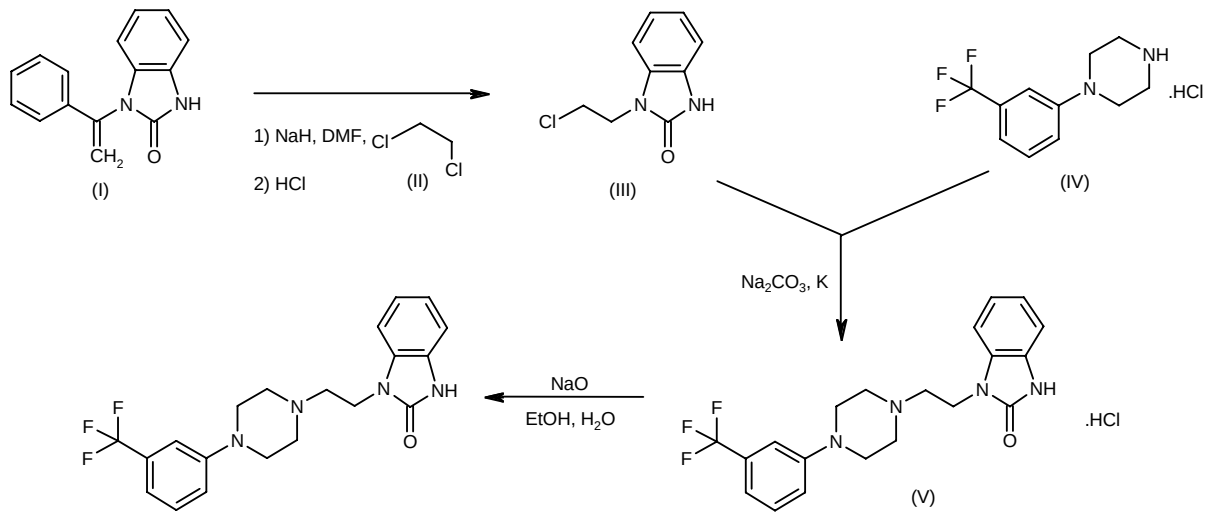
Scheme 1: Synthesis of Flibanserin



hippocampal and cortical receptors. There is growing evidence that the pharmacology of the 5-HT_{1A} receptor subtype may vary according to its localization (4). Several hypotheses have been suggested to explain this phenomenon and are commented upon in the Conclusions.

Several lines of evidence indicate the frontal cortex as a possible target for the therapeutic effect of antidepressants, or as an important area for the occurrence of depression (4). However, none of the purported 5-HT_{1A} agonists (*i.e.*, buspirone, ipsapirone) can be used to stimulate 5-HT_{1A} receptors in the cortex, because they do not behave as agonists in the region (5-7). In fact, the available purported 5-HT_{1A} receptor agonists may behave as full or partial agonists or even as antagonists in the raphe, hippocampus and cortex, respectively. Therefore, no drug is thus far available which can acutely induce the action exerted, or supposed to be exerted, by long-term antidepressant treatment, *i.e.*, 5-HT_2 receptor downregulation and hypersensitivity of 5-HT_{1A} postsynaptic receptors.

Herein we describe a compound which has a double mechanism of action, namely a 5-HT_{1A} agonist and a 5-HT_{2A} antagonist in the frontal cortex, thus capable of exerting at the postsynaptic level after a single dose what current antidepressants may do after repeated administration. This dual mechanism is important because 5-HT_{1A} and 5-HT_2 receptors may coexist in the same cell in the frontal cortex, and their stimulation may exert opposite electrophysiological actions (8). Thus, 5-HT_{1A} receptor-dependent mechanisms in the frontal cortex may clearly be triggered only with a concurrent blockade of 5-HT_2 receptor activity (9, 10).

Due to its immediate effect in the frontal cortex, flibanserin is believed to be the first potential antidepressant exerting therapeutic action more rapidly than any other currently available antidepressant.

Pharmacological Actions

Biochemistry

Flibanserin shows good affinity for 5-HT_{1A} and 5-HT_{2A} receptors (Table I).

Table I: Binding affinity values for BIMT-17 at different receptors.

Receptor	K_i (nM)
5-HT_{1A}	19 ± 2
5-HT_{1B}	>1,000
5-$HT_{1D/E}$	2,656 ± 447
5-HT_{2A}	133 ± 27
5-HT_{2C}	4,431 ± 1,580
5-HT_3	>10,000
5-HT_4	>10,000
5-HT_6	5,360 ± 1,270
5-HT_7	990 ± 90
5-HT uptake site	3,354 ± 499
NE-α_1	523 ± 186
NE-α_2	>10,000
NE-β_1/β_2	>10,000
D_1	7,700 ± 1,149
D_2	>10,000
H_1	4,992 ± 2,410
H_2	>10,000
M_1, M_2, M_3	>10,000
BDZ	>10,000
NMDA/MK-801	>10,000
NMDA/Glycine	>10,000
Opioid-μ	2,424
Nicotinic	>10,000

See reference 7 for methodological details on 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{1D/E}$, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, NE-α_1, NE-α_2, NE-β_1/β_2, D_1, D_2, H_1, H_2, M_1, M_2, and M_3; see 31 for 5-HT_6 and 5-HT_7; see 32 for 5-HT uptake site; see 33 for NMDA/MK-801; see 34 for NMDA/glycine; see 35 for opioid-μ; see 36 for nicotnic.

Table II: Inhibitory effects of flibanserin, 5-HT, 8-OH-DPAT, buspirone, trazodone and S-14671 on forskolin-stimulated adenylyl cyclase in slices of rat hippocampus and frontal cortex.

	Hippocampus		Frontal cortex	
	EC_{50} (nM)	Inhibition (%)	EC_{50} (nM)	Inhibition (%)
5-HT	47 ± 23	25	131 ± 78	16
Flibanserin	317 ± 3	30	913 ± 227	20
8-OH-DPAT	19 ± 3	18	not active as agonist	
Buspirone	142 ± 30	14*	not active as agonist	
Trazodone	Not tested		not active as agonist	
S-14671	1.3 ± 0.2	9**	not active as agonist	

Values represent the mean ± SEM of three separate experiments run in duplicate. *$p < 0.05$; **$p < 0.01$ *versus* 5-HT. See reference 7 for methodological details.

Table III: pK_i values (nM) for tertatolol and 8-OH-DPAT in antagonizing 5-HT and flibanserin-mediated inhibition of forskolin-stimulated adenylyl cyclase activity in frontal cortex.

	5-HT	Flibanserin
Tertatolol	8.70 ± 0.19	8.38 ± 0.21
8-OH-DPAT	8.54 ± 0.16	8.15 ± 0.11

Data are mean values ± SEM from at least three experiments done in duplicate. See reference 7 for methodological details. (Reprinted from Naunyn-Schmied Arch Pharmacol Vol. 352, Borsini, F., Giraldo, E., Monferini, E. et al. *BIMT-17, a 5-HT_{2A} receptor antagonist and 5-HT_{1A} receptor full agonist in rat cerebral cortex*, 276-282, Copyright 1995, with kind permission of Springer-Verlag GmbH & Co. KG.)

Flibanserin behaves as a full agonist in reducing forskolin-stimulated adenylyl cyclase activity in both hippocampal and cortical slices (Table II). Buspirone and 8-OH-DPAT do not behave as agonists in the cortex, a property that has been observed previously (5, 6). The effects of flibanserin on cortical forskolin-stimulated adenylyl cyclase activity seem to be mediated by 5-HT_{1A} receptors (Table III). In fact, these effects are antagonized by tertatolol, which blocks β_2-adrenergic and 5-HT_{1A} receptors, and by 8-OH-DPAT, which, in effect, behaves as an antagonist in our experimental preparation. This antagonism is seen by the values reported in Table III indicating that the activities of tertatolol and 8-OH-DPAT in blocking 5-HT and flibanserin effects are in the same range of affinities reported to bind to 5-HT_{1A} receptors.

Tertatolol also prevented the agonist effect of flibanserin and 5-HT in hippocampal slices (7). In addition, no additive effects on forskolin-stimulated adenylyl cyclase were observed when 100 μM 5-HT was added with 100 μM flibanserin in both cortical and hippocampal slices (7), suggesting that both substances act by the same mechanism. Thus, in contrast to the other 5-HT_{1A} receptor agonists, flibanserin activates 5-HT_{1A} receptor-mediated cAMP effects in both frontal cortex and hippocampus. Moreover, in both brain regions, flibanserin resembles the action of 5-HT.

The 5-HT mimicking action of flibanserin is also observed when the agonist states of the 5-HT_{1A} receptor induced by flibanserin are analyzed. In the cortex, flibanserin recognizes two states of the receptor, 84% of a high affinity state (K_D high = 8.9 nM) and 16% of a low affinity state (K_D low = 3.8 μM), with a ratio of 432 between the two dissociation constants. Similarly, in the same experimental conditions, 5-HT recognizes 73% of a high affinity state of the 5-HT_{1A} receptor, with a ratio between the two constants of dissociation of 567. In contrast, the ratios for buspirone and 8-OH-DPAT are 2129 and 20, respectively.

Flibanserin also shows an antagonist profile at 5-HT_{2A} receptors (Table IV).

Electrophysiology

The selective 5-HT uptake inhibitor fluoxetine (10 mg/kg), administered systemically for 14 days, reduced the number of active cells in the frontal cortex (Fig. 1). This effect was not observed after a single systemic dose of fluoxetine, even when a dose as high as 40 mg/kg was given (11). In contrast, a single systemic administration of flibanserin (16 mg/kg) was able to reduce the number of active cells in frontal cortex (Fig. 1).

Flibanserin reduced the firing rate of the frontocortical cells in a dose-dependent manner (12), and the effect was completely blocked by tertatolol and WAY-100135, both antagonists of the 5-HT_{1A} receptor, suggesting that flibanserin's action was mediated by activation of 5-HT_{1A} receptors (12).

In addition to the inhibition of cells in the frontal cortex, flibanserin also inhibits neurons in hippocampus and

Table IV: Activity of flibanserin in antagonizing 5-HT stimulated phosphatidylinositol turnover in the cerebral cortex.

	K_i (nM)
Flibanserin	113 ± 17
Ritanserin	1.1 ± 0.3

5-HT was used at a concentration of 100 mM. See reference 7 for methodological details.

dorsal raphe. It is interesting that flibanserin behaves as a partial agonist in reducing the firing rate of cells in the hippocampus and acts as a full agonist upon the cells in the frontal cortex and dorsal raphe (13). However, the effect on dorsal raphe does not seem to interfere with the action of flibanserin at the cortical level. In fact, the inhibitory effect on the firing rate of frontocortical cells is still present after the chemical destruction of 5-HT containing neurons brought about by 5,7-dihydroxytryptamine (Fig. 2). This indicates that the effect is achieved through a direct stimulation of postsynaptic receptors (12). This is in sharp contrast with what was observed with fluoxetine, whose effect on the firing rate in prefrontal cortex was found to be completely blocked by the chemical destruction of the 5-HT-containing raphe cortical neurons (14), indicating that this effect is achieved through a presynaptic action. In other words, flibansenrin seems to activate postsynaptic 5-HT_{1A} receptor-mediated electrical effects directly after a single administration, whereas this effect is achieved by fluoxetine indirectly via preynaptic mechanisms and only after chronic administration. 5-HT, as well as flibanserin, when microiontophoretically applied directly to the III-IV layers of the prefrontal cortex, inhibit the electrical activity of neurons (12). This confirms the impression, already obtained by using biochemical techniques, that flibanserin is the first compound which mimics 5-HT in the frontal cortex. In this respect, it is noteworthy that the "claimed" 5-HT_{1A} agonist buspirone,

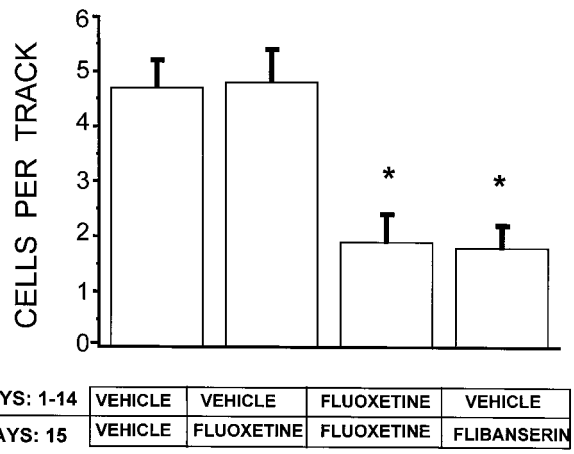


Fig. 1. Effect of acute treatment with fluoxetine and flibanserin and of chronic treatment with fluoxetine on the number of spontaneously active cells in the frontal cortex. Columns represent the mean ± SEM of 8 rats. Acute fluoxetine (10 mg/kg) and flibanserin (16 mg/kg) were given 30 min before the test. Chronic fluoxetine or vehicle was administered once daily for 14 consecutive days. Compounds were given intraperitoneally. *$p < 0.01$ *versus* vehicle group. See reference 11 for methodological details. (Partially reprinted from Eur J Pharmacol Vol. 271, Ceci, A., Fodritto, F., Borsini, F. *Repeated treatment with fluoxetine decreases the number of spontaneously active cells per track in frontal cortex*, 231-234, Copyright 1994, with kind permission of Elsevier Science - NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.)

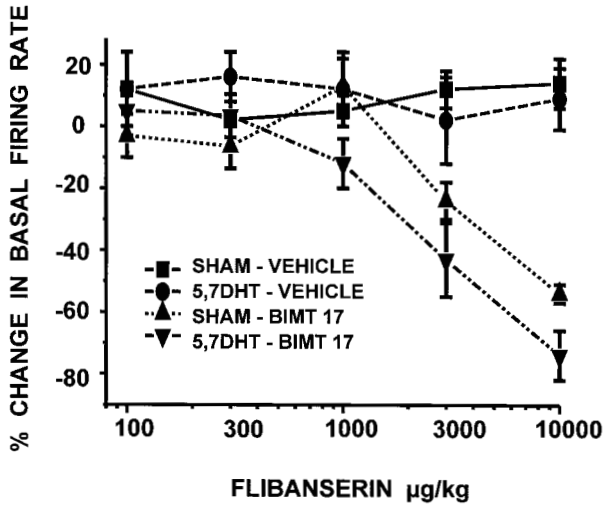


Fig. 2. Effect of 5,7-dihydroxytryptamine (5,7-DHT) on flibanserin-induced inhibition of neuronal firing rate in frontal cortex. 5,7-DHT was given intracerebroventricularly 2 weeks before intravenous flibanserin or vehicle. Each point represents the mean ± SEM of 5-6 rats. See reference 12 for methodological details. (Partially reprinted from Naunyn-Schmied Arch Pharmacol Vol. 352, Borsini, F., Ceci, A., Bietti, G., Donetti, A. *BIMT-17, a 5-HT_{1A} receptor agonist/5-HT_{2A} receptor antagonist, directly activates postsynaptic 5-HT inhibitory responses in the rat cerebral cortex*, 283-290, Copyright 1995, with kind permission of Springer-Verlag GmbH & Co. KG.)

in contrast to flibanserin and 5-HT, increases rather than reduces the firing rate of cortical neurons (12).

The contribution of antagonistic activity of flibanserin upon 5-HT_{2A} receptors on reducing firing rate has not been assessed thus far. 5-HT_2 receptor blockers have been reported to potentiate the inhibitory effect of 5-HT (9, 10). Thus, it is conceivable that the flibanserin-induced inhibitory effect in the frontal cortex may be mediated by both actions, *i.e.*, 5-HT_{1A} receptor agonism and 5-HT_{2A} receptor antagonism.

Behavioral pharmacology

Flibanserin induces signs of the serotonergic syndrome in the rat starting at a dose of 64 mg/kg i.p. (Table V). However, the symptomatology is different from that produced by 8-OH-DPAT, another 5-HT_{1A} receptor agonist, because flibanserin does not provoke forepaw treading. In mice, flibanserin, given i.p. 30 min before the observation period, antagonized the head twitches induced by DOI [1,(2,5-dimethoxy-4-iodophenyl)-2 aminopropane] (1 mg/kg i.p.), a compound which activates 5-HT_2 receptors (15), given 10 min after flibanserin. The ED_{50} value of flibanserin, *i.e.*, the dose that reduces the number of head twitches by 50%, was 4.1 mg/kg (3-5.5; 95% conf. limits).

Flibanserin has been shown to possess antidepressant-like behavior in the forced swimming test and in the

Table V: Effect of flibanserin and 8-OH-DPAT in inducing the serotonergic syndrome in the rat.

Treatment	Dose mg/kg	Scores FP	FT	HA	Total
Flibanserin	8	0	0	0	0
Flibanserin	64	5.0 (2.5-6)	0 (0-1)	2.5 (2-4)	8.5 (4.5-11)
8-OH-DPAT	1	4.5 (3-5)	8.0 (7-9)	0.5 (0.1)	14 (12-15)
8-OH-DPAT	8	6.5 (4-8)	11 (10-13)	4.5 (3-6)	23.5 (21-26)

Values represent the median score with interquartile range summed from 5 observation periods of 30 sec, every 10 min for 50 min from drug administration. The score was as follows: 0 = absent; 1 = equivocal; 2 = definite; 3 = extreme. FP = flat body posture; FT = forepaw treading; HA = hind limb abduction. Four-six animals for each dose were used. Compounds were given intraperitoneally. Total scores were obtained by summing the scores of each component.

mild chronic stress test in mice (16-18), in the learned helplessness paradigm (19), in mild chronic stress test in rats (18), and in bulbectomized rats (19).

The effect of a single administration of flibanserin (16 mg/kg i.p.) in the forced swimming test was antagonized by 10 mg/kg WAY-100135, a 5-HT_{1A} antagonist, but not by depletion of 5-HT, brought about by inhibition of 5-HT synthesis by parachlorophenylalanine or by chemical destruction with the neurotoxin 5,7-dihydroxytryptamine (16). These findings again indicate that flibanserin directly activates postsynaptic 5-HT_{1A} receptors without interfering with 5-HT presynaptic mechanisms. Interestingly, in similar experimental conditions, the effect of fluoxetine was reduced by *para*-chlorophenylalanine (20), suggesting once again the difference in action between flibanserin and a presynaptic acting antidepressant. Furthermore, the effect of flibanserin in the forced swimming test was antagonized by α-methyl-p-tyrosine, an inhibitor of catecholamine synthesis, and by sulpiride, a dopamine D_2 receptor antagonist (16). Since flibanserin does not have affinity for dopamine D_2 receptors, it is conceivable that the stimulation of 5-HT_{1A} receptors may activate dopamine-containing neurons which, in turn, excite dopamine D_2 receptors.

In the forced swimming test, the 5-HT_{2A} component of flibanserin does not seem to play a major role, since a 5-HT_2 receptor agonist (DOI) did not affect flibanserin's action (16), even at high doses which should have counteracted the blocking action at the 5-HT_2 receptors.

Interestingly, the doses of flibanserin producing 50% of the effect in the same animal species (mouse), using the same route of administration (i.p.), in two different

Table VI: Effect of acute flibanserin and imipramine, and of repeated imipramine in the learned helplessness paradigm.

Group	`Treatment	Dose mg/kg	No. of escape failures	
			Median	Interquartile range
Acute flibanserin				
IS-	Saline	0	5.5#	1.5 - 11.0
IS+	Saline	0	12.0	9.5 - 15.0
IS+	Flibanserin	24	7.5	4.0 - 13.5
IS+	Flibanserin	48	3.0*	0.0 - 14.0
Acute Imipramine				
IS-	Saline	0	6.5#	3.0 - 12.5
IS+	Saline	0	14.0	12.0 - 14.5
IS+	Imipramine	4	13.5	6.0 - 15.0
IS+	Imipramine	8	13.0	7.5 - 14.5
IS+	Imipramine	16	13.5	12.0 - 14.5
Repeated imipramine				
IS-	Saline	0	10.5#	8.5 - 14.0
IS+	Saline	0	15.0	15.0 - 15.0
IS+	Imipramine	4	15.0	12.5 - 15.0
IS+	Imipramine	8	5.5*	3.5 - 9.0

Values represent median and interquartiles of 16 rats. IS- represents the vehicle-treated group of animals which did not undergo the shock on the first session of the test. IS+ represents the vehicle-treated animals which underwent the shock on the first session of the test. Both flibanserin and imipramine were only given to animals which underwent the shock on the first session of the test. Acute flibanserin was given orally and imipramine was given intraperitoneally 30 min before testing. #$p < 0.05$ and $p < 0.01$ *vs* IS+. Repeated imipramine means that it was given 6 times. The table shows that acute flibanserin as well as repeated imipramine, but not acute imipramine, improved the behavior of animals in making errors trying to avoid the electrical shock, during the second session of the test. No treatment increased the intertrial crossings. See reference 19 for methodological details.

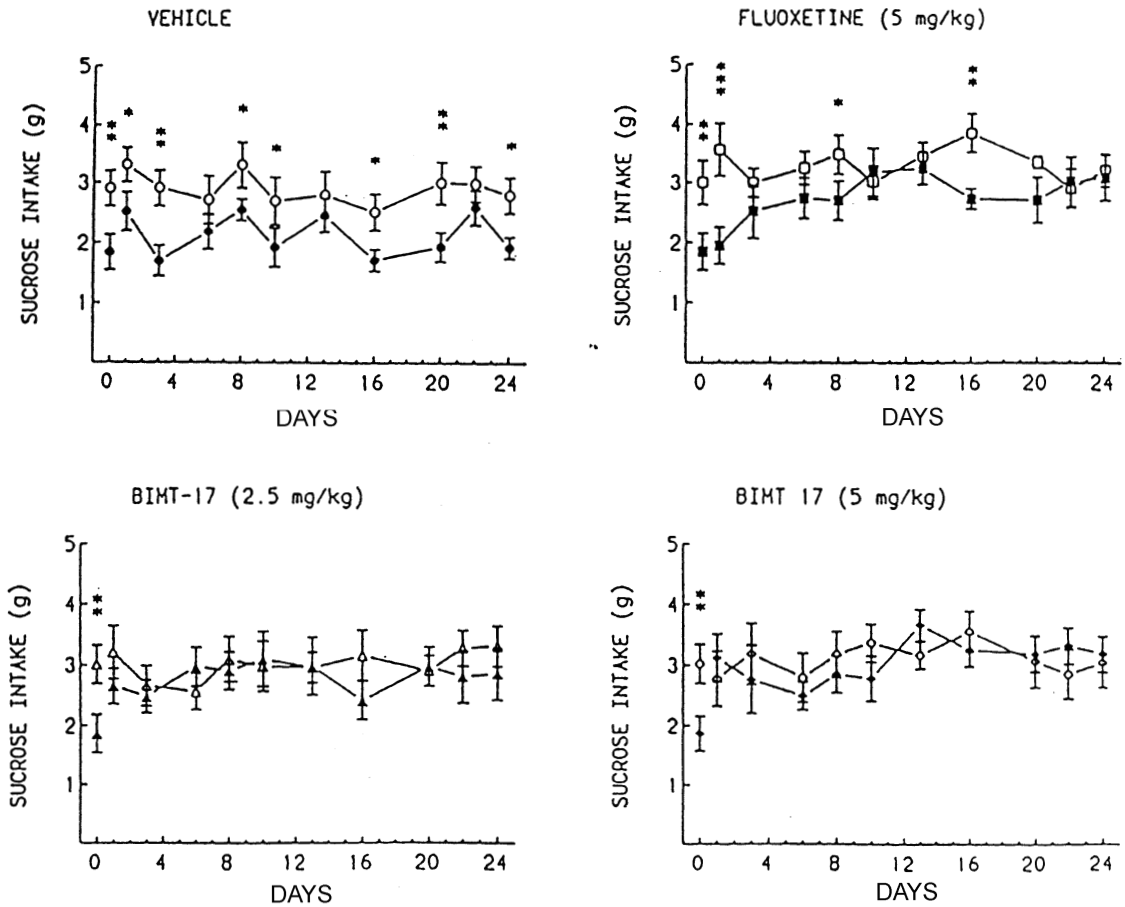


Fig. 3. Effect of flibanserin (BIMT-17) and fluoxetine in the chronic mild stress procedure in mice. Open and filled circles indicate the sucrose intake of unstressed and stressed animals, respectively. Sucrose intake was measured for 1 h at noon, and drug treatment was given intraperitoneally in the afternoon, for 24 consecutive days. The open and filled circles on day 0 represent the sucrose intake of unstressed and stressed animals before drug treatment. See reference 18 for methodological details. *$p < 0.05$; **$p < 0.01$ between unstressed and stressed animals on the same day. (Reprinted from Willner, P. *Animal models of depression: validity and applications.* In: Depression and Mania: From Neurobiology to Treatment. Eds. G. Gessa, W. Fratta, L. Pani, G. Serra, 19-41, Copyright 1995, with kind permission of Lippincott-Raven Publishers, Philadelphia, USA.)

behavioral models (forced swimming test for 5-HT_{1A} receptor activation and DOI-induced head twitches for 5-HT_{2A} receptor antagonism) are about 16 and 4 mg/kg, respectively. Thus, it seems that in vivo the proportion in effective doses between the 5-HT_{1A} agonism and 5-HT_{2A} antagonism is well balanced. This may be important since it is generally believed that only about 20% of receptor occupancy is necessary to trigger agonist activity, whereas about 80% of receptor occupancy is required to exert antagonist action.

An antidepressant-like effect with flibanserin was also obtained in the bulbectomized rat after chronic administration (10 and 20 mg/kg i.p. once daily) for 14 consecutive days (19). On the other hand, in contrast to classical antidepressants, flibanserin was not active in the DRL 72-s (differential-reinforcement-of-low rate 72-sec) test (19).

According to our working hypothesis, as expressed in the Introduction, flibanserin, as a first direct postsynaptic 5-HT_{1A} receptor agonist, should exert an antidepressant effect within a very short period of time. In order to assess this possibility, we chose two animal paradigms which have been reported to be sensitive to repeated but not single administration of antidepressants: the learned helplessness test (19) and the chronic mild stress procedure (17, 18). Flibanserin was active in both tests reversing either the learned helplessness behavior (Table VI) or the stress-induced anhedonia (Fig. 3) after a single administration, whereas other antidepressants required repeated administration. The efficacy of flibanserin was continuously maintained for 3 weeks in the chronic mild stress paradigm (18), suggesting that flibanserin-induced antianhedonic effects do not undergo desensitization.

Conclusions

Research into the mechanisms of action of antidepressants has been focused mainly on understanding

how to increase the synaptic cleft concentration of monoamines. Only in the past few years has attention been addressed to understanding in vivo mechanisms. These studies have brought to light the crucial role played by somatic presynaptic autoreceptors (21), which permit monoamine uptake blockers to increase the synaptic cleft monoamine concentration in terminal brain regions (22, 23). To do this, however, monoamine uptake inhibitors must first desensitize somatic presynaptic autoreceptors, an action that may require as much as 2-3 weeks of treatment.

Several current clinical approaches are aimed at shortening the time within which somatic presynaptic autoreceptors desensitize. Thus, several drug combinations have been used, such as pindolol and SSRIs (2, 3, 24), or trazodone and fluoxetine or pindolol (25). The objective of these cotreatments is to increase 5-HT in the synaptic cleft in terminal brain regions within a shorter period of time (by preventing presynaptic somatic autoreceptor desensitization). However, it is still not understood which postsynaptic receptor is stimulated by 5-HT. First, a role for 5-HT_{1A} receptors seemed to be excluded by the fact that buspirone, a claimed 5-HT_{1A} agonist, did not exert a rapid antidepressant effect. The finding that buspirone is not a 5-HT_{1A} receptor agonist at the cortical level, and is only a partial agonist at the hippocampal level, could explain its failure to shorten the time lag of its antidepressant effect.

The fact that flibanserin is the first compound which is a full agonist in the cortex and hippocampus opens new horizons. The pharmacology of flibanserin is different from that of the other 5-HT_{1A} agonists, a finding which has important repercussions. One cannot exclude that 5-HT_{1A} receptors may exist as different subtypes, as suggested by the discovery that there are three different mRNAs for the 5-HT_{1A} receptor in the rat brain (26) and two mRNAs in the human brain (27). In addition, it has been reported that antibodies against the second extracellular loop and the third intracellular loop of the 5-HT_{1A} receptor localize the receptor itself to different parts of the cell (28). What is intriguing is that the cDNA encoding the 5-HT_{1A} receptor has no introns (29), and recently multiple 5-HT_{1A}receptor transcripts have been described to arise from variations of the 3'-untranslated region (3'UTR). Alternatively, there is the possibility that flibanserin binds to site(s) on the 5-HT_{1A} receptor differently from that bound by the other 5-HT_{1A} agonists, thus being capable of activating G-proteins differently (30).

That the pharmacology of 5-HT_{1A} receptors is complex is further demonstrated by the fact that flibanserin in the hippocampus acts as a full agonist in inhibiting forskolin-stimulated adenylyl cyclase (12) and a partial agonist in inhibiting neuronal firing rate (13).

Even if the exact molecular mechanisms of flibanserin still need to be elucidated, its special pharmacology makes it a unique drug. It not only can mimic antidepressant-like action but can also induce after a single dose some of the effects exerted by antidepressants after repeated administration. Only clinical trials will demonstrate whether these mechanisms are relevant in humans, and if so, flibanserin could be the first antidepressant available for the short-term treatment of depressive disorders.

Manufacturer

Boehringer Ingelheim (IT).

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