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Effects of JL 3, a putative antidepressant, on rat noradrenergic and serotonergic systems

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Abstract

Using in vitro electrophysiological procedures, we confirm the inhibitory effect of 10-(4-methylpiperazin-1-yl)pyrido[4,3-*b*][1,4]benzothiazepine (JL 3), on dorsal raphe serotonergic (IC_{50} = 14 μM) and noradrenergic neurons (IC_{50} = 4.5 μM). The effect on dorsal raphe neurons was reduced by *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide (WAY-100635), suggesting the importance of 5-HT_{1A} receptor stimulation. Yohimbine, and ritanserin, to a lesser extent, blocked the inhibitory effect of JL 3 on locus coeruleus neurons indicating that α_2-adrenoceptors and 5-HT_{2A} receptors may be implicated in the effects. Because of its negligible α_2-adrenoceptor affinity, the effect of JL 3 on locus coeruleus neurons, would have to be indirect. JL 3 may interfere with the norepinephrine transporter site (IC_{50} = 0.34 μM). JL 3 tended to reinforce the hypertensive effect of norepinephrine, while it strongly inhibited the hypertensive effect of tyramine, further indicating an interaction at the norepinephrine transporter site level.

Keywords: Electrophysiology; Antidepressant; 5-HT_{1A} receptor; α_2-Adrenoceptor; Tyramine; Norepinephrine transporter; Pyridobenzoazepine

1. Introduction

Behavioral models such as the open-field test in the rat and forced swimming test in the mouse indicate an antidepressant profile of 10-(4-methylpiperazin-1-yl)pyrido[4,3-*b*][1,4]benzothiazepine (JL 3) (Bruhwyler et al., 1995). These behavioral effects of JL 3 are supported by in vivo electrophysiological experiments conducted in rats. Thus, JL 3, like several tricyclic antidepressant drugs (Scuvée-Moreau and Dresse, 1979), acutely reduced the firing rate of dorsal raphe serotonergic (ID_{50} = 3.87 mg/kg, i.v.) and locus coeruleus noradrenergic (ID_{50} = 2.63 mg/kg, i.v.) neurons (Liégeois et al., 1996).

The inhibitory effect of JL 3 on the firing rate of central neurons might be based on several mechanisms. JL 3 has a significant affinity for 5-HT_{1A} receptors (K_i = 323 nM) (Liégeois et al., 1996), which could be the basis for its effect on dorsal raphe neurons (Sprouse and Aghajanian, 1987). The 5-HT_{2A} affinity of JL 3 (K_i = 282 nM) (Liégeois et al., 1994), might explain its inhibitory effect on locus coeruleus neurons since postsynaptic 5-HT_{2A} receptors have been shown to control the spontaneous discharge of locus coeruleus neurons (Gorea and Adrien, 1988). A reduction of activity of locus coeruleus can also be induced by α_2-adrenoceptor agonists such as clonidine (Svensson et al., 1975; Marwaha and Aghajanian, 1982). However, the affinity of JL 3 for α_2-adrenoceptors is negligible (K_i > 10,000 nM) (Liégeois et al., 1996). Finally, the inhibitory effect of several tricyclic antidepressant drugs was found to be correlated with their potency to inhibit the in vitro neuronal uptake of 5-HT and norepinephrine (Quinaux et al., 1982).

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To further understand the mechanisms involved in the inhibitory effect of JL 3 on the firing rate of locus coeruleus and dorsal raphe neurons, we used rat brain slice preparations according to previously described methods (Seutin et al., 1990). As our electrophysiological results suggested that a part of the action of JL 3 depended on an inhibition of norepinephrine neuronal uptake, we also examined the influence of JL 3 on this uptake in vivo through an indirect approach: the influence of the drug on the hypertensive effects of norepinephrine and tyramine (Iversen, 1967).

2. Materials and methods

2.1. Animals

Wistar rats reared in the breeding farm of our laboratory (male weighing 150–250 g for in vitro electrophysiological experiments, and both sexes weighing 250 g for physiological studies) were used. All the experiments were conducted according to the guidelines of the National Institutes of Health (NIH publication No. 80-23, revised 1978).

2.2. In vitro electrophysiological studies

Animals were deeply anaesthetized with chloral hydrate (400 mg/kg, i.p.) and given 100% of oxygen to breathe for 5 min. After decapitation, the brain was quickly removed and cooled in ice-cold artificial cerebro-spinal fluid (ACSF), which had the following composition (in mM): NaCl, 130; KCl, 5; NaH_2PO_4, 1.25; $NaHCO_3$, 24; D-glucose, 10; $CaCl_2$, 2; $MgSO_4$, 1.25. A piece of brainstem was prepared and cut in transverse sections by means of a vibratome. The thickness of the slices was about 0.4 mm. A slice containing either the locus coeruleus or the dorsal raphe area was placed on a nylon mesh in a recording chamber (volume 0.5 ml). The tissue was held in position by several short pieces of platinum. The slice was completely immersed in a continuously flowing ($\pm$2 ml/min), heated ($\pm$35°C) solution of the same composition as indicated above.

Extracellular recordings were made using glass micropipettes filled with ACSF and having an impedance of 5–10 MΩ and a tip diameter of 2–5 μm. Action potentials were amplified and displayed on a Tektronix oscilloscope. The signals were also introduced into an amplitude discriminator and counted every 10 s by a digital counter.

Both noradrenergic and serotonergic neurons were identified with electrophysiological and pharmacological criteria as previously described (Seutin et al., 1990). To record from serotonergic neurons, the α_1-adrenoceptor agonist, phenylephrine (10 μM), was continuously superfused in order to evoke a regular spiking activity (1–3 Hz).

In all experiments, a 5-min control period was taken in order to assess the stability of the firing rate. Drugs were superfused using three-way taps so that the flow rate remained constant. Each concentration was superfused until the equilibrium was obtained (10 min or less). When antagonists (ritanserin, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide (WAY-100635), and yohimbine) were used, they were firstly superfused alone during 10 min in order to reach their steady-state concentration in the tissue before application of agonists.

2.3. Recordings of the mean systemic blood pressure

Rats were anaesthetized with sodium pentobarbital (45 mg/kg, i.p.). A tracheotomy was performed and the mean arterial blood pressure was recorded from a carotid artery with a Harvard 50-8952 transducer connected to a Harvard Universal oscillograph, and coupled to a mercury manometer. After i.v. injection of heparin (250 U/kg) through a catheter placed into a jugular vein, the hypertensive effects of norepinephrine (0.4, 0.8 or 1.6 μg/kg) and of tyramine (100, 200 and 300 μg/kg) were measured. Then, JL 3 (1, 5 or 10 mg/kg, i.v.) was injected and 5 min later, another set of three injections of norepinephrine and of tyramine was performed.

2.4. Drugs

JL 3 was synthetized according to previously described methods (Liégeois et al., 1994). Norepinephrine and tyramine were purchased from Aldrich. Buspirone, clonidine, desipramine, ritanserin and yohimbine were obtained from Bristol Myers Squibb, Boehringer Ingelheim, Novartis, Janssen Pharmaceutica, and Hoechst Marion Roussel, respectively. WAY-100635 was a generous gift of Prof. H. Wikström (University of Groningen, Department of Medicinal Chemistry, NL). For physiological studies, JL 3 was dissolved in 50% propyleneglycol/water mixture while the sympathomimetic amines were dissolved in saline. For electrophysiological experiments, stock solutions of JL 3 were prepared in dimethylsulfoxide (DMSO). The final concentration of DMSO never exceeded 1%. Control experiments showed that this concentration of DMSO had no effect on the firing rate of the cells. Stock solutions of the other compounds (100 to 1000 times the final concentration) were made in water.

2.5. Statistical analysis

In vitro electrophysiological data were analyzed as follows. The percent inhibition of firing rate induced by each concentration of agonist was calculated. Concentration–response curves were fitted using Kaleidagraph software according to the following equation: $E = E_{max}/(1 + (IC_{50}/x)h)$, where x is the concentration of drug and h the Hill coefficient. Results were expressed as means ($\pm$SEM). Means were statistically compared using Student's *t*-tests. Differences were considered significant when $P < 0.05$.

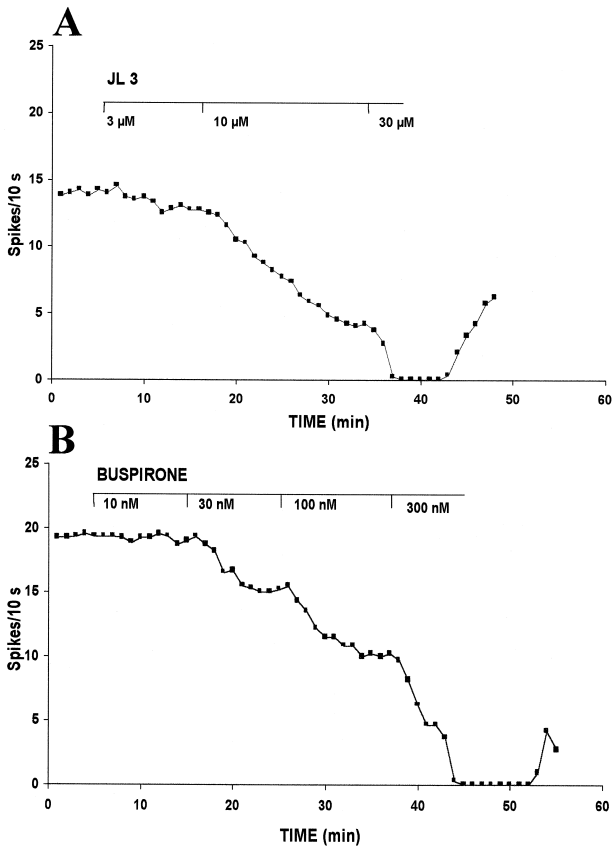

Fig. 1. Inhibitory effect of JL 3 (A) and buspirone (B) on the neuronal activity of the dorsal raphe. Infusion periods of drugs are represented by bar above the curve.

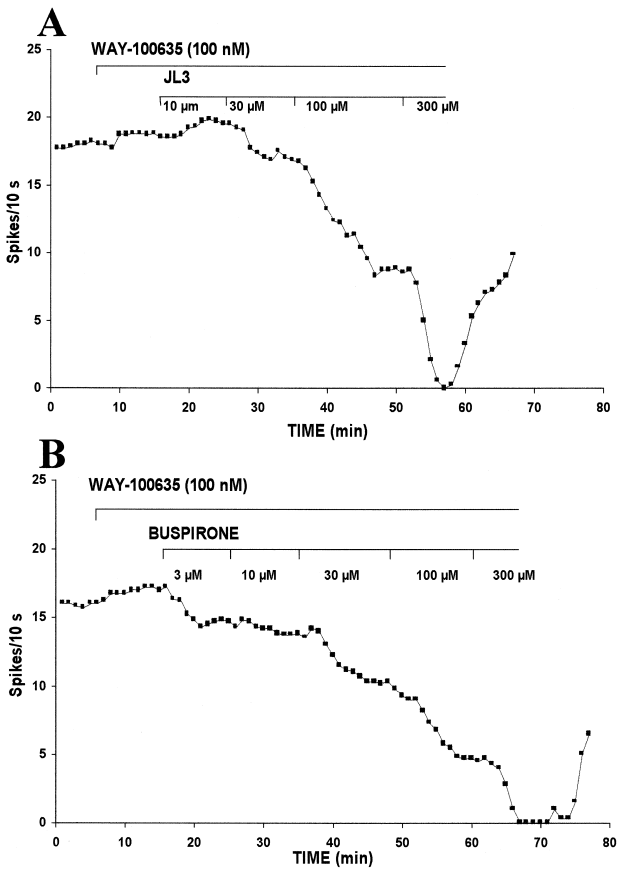

Fig. 2. Interaction of WAY-100635, a 5-HT_{1A} antagonist on the inhibitory effect of JL 3 (A) and buspirone (B) on the neuronal activity of the dorsal raphe. Compared to Fig. 1A,B the curves were shifted on the right. pK_b for JL 3 and buspirone are 7.44 and 9.93, respectively. Infusion periods of drugs are represented by bar above the graph.

The effects of JL 3 on the systemic blood pressure and on the hypertension induced by norepinephrine or tyramine were evaluated using an analysis of variance (ANOVA) for repeated measurements followed when significant ($P < 0.05$) by post hoc Bonferonni adjusted paired *t*-tests.

3. Results

3.1. Effect of JL 3 on the firing activity of dorsal raphe neurons

JL 3 had an inhibitory effect on dorsal raphe neurons activity when superfused alone (Fig. 1A). The mean IC_{50} was 14 μM. A similar effect had previously been observed using in vivo experiments (Liégeois et al., 1996). In comparison, buspirone, a 5-HT_{1A} receptor agonist, also decreased the activity of dorsal raphe neurons (Fig. 1B) and had an IC_{50} equal to 0.042 μM (Table 1). When WAY-100635 (0.1 μM), a 5-HT_{1A} receptor antagonist, was simultaneously administered, the inhibitory effect for

Table 1
Inhibitory potency of JL 3 and buspirone on the firing rate of dorsal raphe neurons in brain slices. IC_{50}: mean total dose required to produce a 50% inhibition of the frequency of discharge; n = number of experiments

Drugs	IC_{50} ± SEM (n)	pK_b
JL 3	14 ± 4 μM (8)	
JL 3 + WAY-100635 (100 nM)	53 ± 9 μM (6)*	7.44
Buspirone	0.042 ± 0.010 μM (8)	
Buspirone + WAY-100635 (100 nM)	36 ± 11 μM (6)*	9.93

* $P < 0.001$; Student's *t*-tests.

Table 2
Inhibitory potency of JL 3 on the firing rate of locus coeruleus neurons in brain slices compared to that of clonidine and desipramine
IC_{50}: mean total dose required to produce a 50% inhibition of the frequency of discharge; n = number of experiments.

Drugs	IC_{50} ± SEM (n)	pK_b
JL 3	4.5 ± 1 μM (9)	
JL 3 + yohimbine (1 μM)	48 ± 9 μM (8)*	6.98
Clonidine	0.004 ± 0.001 μM (6)	
Clonidine + yohimbine (1 μM)	0.263 ± 0.030 μM (6)*	7.81
Desipramine	0.425 ± 0.066 μM (6)	
Desipramine + yohimbine (100 nM)	8.7 ± 3.0 μM (6)**	8.29
JL 3 + ritanserin (1 μM)	9.8 ± 1.8 μM (6)**	6.07

* $P < 0.001$; Student's *t*-tests.
** $P < 0.05$; Student's *t*-tests.

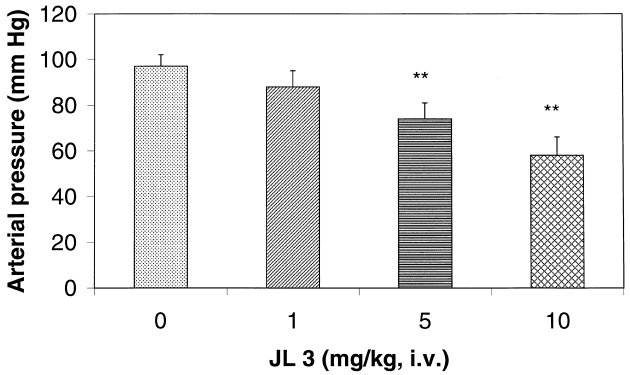

Fig. 3. Effect of JL 3 (i.v. administration) on the rat arterial pressure. Results are given as means (±SEM). Statistical significance was evaluated using ANOVA for repeated measures followed when significant by Bonferonni adjusted paired t tests ($^{**}P < 0.01$).

both compounds was markedly attenuated (Fig. 2A,B). The mean IC_{50} increased to 53 μM and 36 μM for JL 3 and buspirone, respectively (Table 1). These variations were found to be highly significant ($P < 0.001$). When perfusion of drug was stopped the neuronal activity recovered quickly (Fig. 1A,B and Fig. 2A,B).

3.2. Effect of JL 3 on the firing activity of locus coeruleus neurons

JL 3 inhibited the neuronal activity of locus coeruleus neurons (Table 2). The IC_{50} was equal to 4.5 μM while clonidine, an α_2-adrenoceptor agonist, had an IC_{50} equal to 0.004 μM. For both compounds, the inhibitory effect was highly significant ($P < 0.001$). The presence of yohimbine (1 μM), an α_2-adrenoceptor antagonist, significantly reduced the inhibitory effect of both compounds ($P < 0.001$). The IC_{50}s were 48 and 0.263 μM for JL 3 and clonidine, respectively. In similar neuronal preparation, desipramine, a norepinephrine reuptake inhibitor, presented an IC_{50} equal to 0.425 μM which was significantly reduced up to 8.7 μM ($P < 0.05$) in the presence of yohimbine (100 nM).

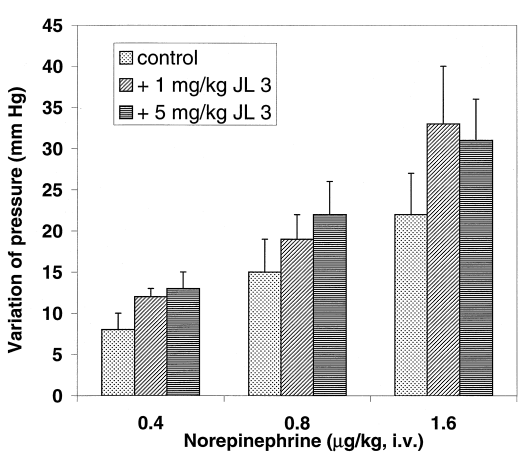

Fig. 4. Interaction between JL 3 (i.v. administration) and norepinephrine on the rat arterial pressure. Results are given as means (±SEM). Statistical significance was evaluated using ANOVA for repeated measures followed when significant by Bonferonni adjusted paired t tests.

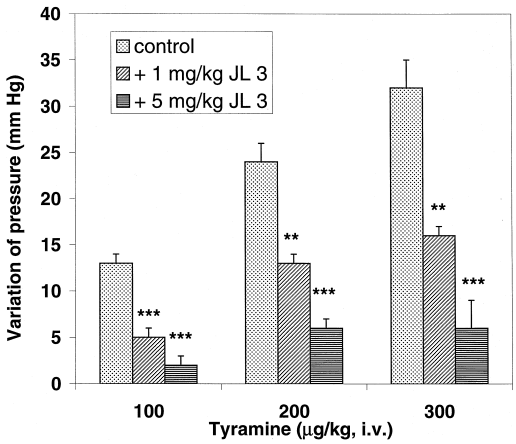

Fig. 5. Interaction between JL 3 (i.v. administration) and tyramine on the rat arterial pressure. Results are given as means (±SEM). Statistical significance was evaluated using ANOVA for repeated measures followed when significant by Bonferonni adjusted paired t tests ($^{**}P < 0.05$; $^{***}P < 0.01$).

When JL 3 and ritanserin (1 μM), a 5-$HT_{2A/2C}$ receptor antagonist, were superfused simultaneously, the IC_{50} for JL 3 was moderately but significantly increased up to 9.8 μM ($P < 0.05$).

3.3. Influence of JL 3 on the hypertensive effects of norepinephrine and tyramine

When administered alone, JL 3 significantly reduced ($P < 0.0001$; ANOVA) the mean arterial pressure in a dose-related manner (Fig. 3). Its effect was significant at 5 and 10 mg/kg ($P = 0.003$ and $P = 0.008$, respectively; Bonferonni tests) but nonsignificant ($P = 0.053$; Bonferonni tests) at 1 mg/kg. The solvent (50% aqueous propyleneglycol solution) had no significant effect on the mean blood pressure (data not shown).

Although JL 3 (1 and 5 mg/kg) tended to potentiate in a dose-related manner the hypertensive effect of norepinephrine (0.4, 0.8 and 1.6 μg/kg), this potentiating effect remained nonsignificant ($P > 0.05$; ANOVA) (Fig. 4).

In a second experiment, JL 3 significantly ($P < 0.0001$; ANOVA) reduced the hypertensive effects of tyramine in a dose-related manner (Fig. 5). The decrease was significant ($P < 0.01$; Bonferonni tests) at 1 mg/kg and at 5 mg/kg for the three doses of tyramine (100, 200 and 300 μg/kg).

4. Discussion

In the present study, we observed an inhibitory effect of JL 3 on isolated preparations of dorsal raphe (Fig. 1; Tables 1 and 2) and locus coeruleus (Tables 1 and 2).

These effects indicated that JL 3 either directly inhibited dorsal raphe and locus coeruleus neuronal activity or by indirect neuronal circuits located in these areas. Previously, we reported that JL 3, like other antidepressant drugs, reduced in vivo the firing rate of dorsal raphe and locus coeruleus neurons in rats (Liégeois et al., 1996). This was correlated with the antidepressant profile of JL 3 in behavioural studies performed in the open-field and forced swimming tests, respectively in rats and mice (Bruhwyler et al., 1995).

What are the receptors implicated in the effects of JL 3 on these neuronal areas? JL 3 presents significant affinity for a few receptors (Table 3) that could be implicated in the behavioural and electrophysiological effects of this drug. This is the case for 5-HT_{1A} receptors ($K_i = 323$ nM), 5-HT_{2A} receptors ($K_i = 282$ nM) and also norepinephrine transporter site ($IC_{50} = 340$ nM).

The spontaneous activity of dorsal raphe neurons is known to be modulated by 5-HT_{1A} cell body autoreceptors (Vergé et al., 1985; Weismann-Nanopoulos et al., 1985). Compounds which act as agonists or partial agonists at 5-HT_{1A} receptors such as 8-hydroxy-2-*N*,*N*-propylaminotetralin (8-OH-DPAT) (Blier and de Montigny, 1987), buspirone (VanderMaelen et al., 1986), and BMY 14802 (VanderMaelen and Braselton, 1990) can potently inhibit the firing of serotonergic dorsal raphe neurons (Aghajanian et al., 1968; Sprouse and Aghajanian, 1986, 1987; VanderMaelen et al., 1986; Blier and de Montigny, 1987). In the present study, buspirone, a 5-HT_{1A} receptor agonist, effectively decreased the activity of dorsal raphe neurons (Fig. 1; Table 1), and this inhibition was reduced by the action of WAY-100635, a 5-HT_{1A} receptor antagonist (Fig. 2; Table 1) ($pK_b = 9.93$). Similarly, the inhibitory effect of JL 3 was decreased by the same antagonist ($pK_b = 7.44$). It should be noted, however, that the displacement of the curve of JL 3 by the action of WAY-100635 was much smaller than for buspirone. These results suggest that 5-HT_{1A} receptor stimulation cannot explain alone the effect of JL 3 in these cells. Moreover, JL 3 has no affinity for the 5-HT transporter site (Table 3). The results of this investigation might indicate that JL 3 acts as a relatively weak agonist or partial agonist at central 5-HT_{1A} receptors. It is also known that α_1-adrenoceptor antagonists can produce inhibition of these dorsal raphe neurons (Baraban and Aghajanian, 1980; Menkes et al., 1981) but JL 3 binds weakly to α_1-adrenoceptors ($K_i = 1{,}740$ nM).

Table 3
In vitro binding profile of JL 3

Receptors	K_i (nM)
D_1	>1000[a]
D_2	>1000[a]
α_1-adrenoceptor	1740[b]
α_2-adrenoceptor	$>10{,}000$[b]
5-HT_{1A}	323[c] (370)[b]
5-HT_{2A}	282[a] (>1000)[b]
5-HT_{2c}	2300[b]
Transporter sites	**IC_{50} (nM)**
Dopamine	$>10{,}000$[b]
Norepinephrine	340[b]
Serotonin	$>10{,}000$[b]

[a] From Liégeois et al. (1994).
[b] Data obtained using methodologies reported in Schotte et al. (1996).
[c] From Liégeois et al. (1996).

The inhibitory effect of JL 3 on locus coeruleus neurons (Table 2) was reduced by ritanserin, a 5-$HT_{2A/2C}$ receptor antagonist ($pK_b = 6.07$), and also by yohimbine, an α_2-adrenoceptor antagonist ($pK_b = 6.98$). Thus, the effect of JL 3 might be mediated by at least two mechanisms. A small part of its effect may depend on the stimulation of 5-HT_{2A} receptors, and a major part may depend on the activation of α_2-adrenoceptors. The 5-HT_{2A} receptor and α_2-adrenoceptor affinity of JL 3 is 282 nM and greater than 10,000 nM, respectively. Thus, an indirect effect of JL 3 on α_2-adrenoceptors, such as blockade of the norepinephrine uptake, is more likely leading to increase norepinephrine. Indeed, the blockade of such sites increases the stimulation of α-adrenoceptors by endogenous and exogenous norepinephrine (Iversen, 1967). Recent in vitro investigations showed that JL 3 had significant effect on norepinephrine transporter site ($IC_{50} = 340$ nM). To confirm the effect of JL 3 on this site, we used a classical indirect approach, e.g., the influence of a drug on the hypertensive effect of norepinephrine and tyramine, an indirect-acting amine (Guimaraes and Trendelenburg, 1985). We observed that JL 3 strongly decreased the hypertensive effect of tyramine (Fig. 5) and simultaneously tended to increase the hypertensive effect of norepinephrine (Fig. 4) like other inhibitors of the neuronal uptake of catecholamines such as cocaine (Iversen, 1967). These results suggest that JL 3 could act in the central nervous system, like several tricyclic antidepressants (Quinaux et al., 1982), to potentiate the action of biogenic amines by blockade of their reuptake at nerve terminals. As mentioned above, for the right shift of the curve in presence of an antagonist compound, e.g., WAY-100635, ritanserin or yohimbine, the displacement of the curve in the locus coeruleus was weaker for JL 3 than for the other reference drugs (clonidine or desipramine) (Table 2). This result suggests that additional mechanisms might be involved in the inhibitory effect of JL 3 in the locus coeruleus.

In vitro data indicated that JL 3 was three times more active in inhibiting the firing activity of locus coeruleus neurons compared to that of dorsal raphe neurons while in vivo (Liégeois et al., 1996) the difference was smaller (± 1.5). Such difference could be due to the reciprocal interaction between locus coeruleus and dorsal raphe nucleus since numerous studies have documented several interactions between noradrenergic and serotonergic systems (Anderson et al., 1977; Baraban and Aghajanian, 1980; Haddjeri et al., 1997). In the in vitro preparations,

indirect mechanisms might be limited due to reduced neuronal connections.

In conclusion, the results obtained with isolated preparations of dorsal raphe and locus coeruleus neurons confirm the inhibitory effect of JL 3 previously observed in vivo (Liégeois et al., 1996). JL 3 may inhibit the activity of dorsal raphe neurons by an agonist effect on 5-HT_{1A} receptors while the inhibition of the firing activity of locus coeruleus neurons may result from two main effects: direct stimulation of 5-HT_{2A} receptors and indirect activation of α_2-adrenoceptors through blockade of norepinephrine neuronal uptake. However, due to the differences observed between JL 3, and various reference drugs in terms of displacement of the effect by antagonists, other undefined receptors could be implicated in the inhibitory effect of JL 3 on both neuronal preparations.

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