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Selective α-adrenoceptor blocking action of melperone

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ABSTRACT High selective α-adrenoceptor blocking action of melperone was investigated in pithed rats and isolated rat vas deferens. The selectivity ratio of α_1/α_2 for adrenoceptor blockade of melperone, prazosin and yohimbine were estimated to be 1542, 3304 and 0.0225, respectively. The value of pA_2 of melperone (α_2, 6.14) was lower than that of prazosin (6.25) and much lower than that of yohimbine (8.35). The results indicate that melperone is a drug with higher α_1-adrenoceptor blocking action, comparable to prazosin.

KEY WORDS melperone; adrenergic alpha receptor blockaders; pithed rats; vas deferens; prazosin

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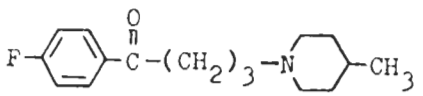
Melperone is a neurolptic, which also reduces peripheral resistance and depresses the arterial blood pressure in animal and human[1]. We found that this agent reduced

the blood pressure rapidly in anesthetized normotensive rats mainly through its peripheral vasodilator effect. In contrast to the classical vasodilator hydralazine, melperone didn't induce the reflex tachycardia, but rather induced a bradycardia when the blood pressure decreased (unpublished data).



Melperone

Melperone possesses α_1-adrenoceptor blocking action in pithed rats[2]. Taking the blood pressure elevation by clonidine in pithed rat as an index of postsynaptic α_1-adrenoceptor excitation, and the heart rate slowing responding to sympathetic stimulation as an index of presynaptic α_2-adrenoceptor excitation. Petersen[3] evaluated the blocking action of melperone on pre- and post-synaptic adrenoceptors. However, the recent findings of postsynaptic α_2-adrenoceptor mediated vasoconstriction make the analysis of α-adrenoceptors more complicated. Both α_1- and α_2-adrenoceptor subtypes coexisted at the sympathetic nerve endings, and both subtypes mediated vasoconstriction[4] and could be excited by clonidine[5]. So, the estimation of the selectivity ratio of α_1/α_2 of melperone made by Petersen is unjustifiable and no precise ratio had been reported so far. Melperone may be a new type of potential antihypertensive drug and it is interesting to assess its α_1/α_2 selectivity ratio for exploring its therapeutic value and side effects.

MATERIALS AND METHODS

Pithed rats Normotensive rats (250± SD 40 g) under pentobarbital anesthesia and artificial respiration were pithed via the orbit[6]. After the blood pressure was stabilized, logarithmic cumulated dose-pressor response curve of methoxamine was established, and 10 min after the administration of melperone (0.1 mg/kg iv), the above curve was reestablished.

The other groups of rats were bilaterally adrenalectomized first and then pithed with an enameled rod with the tip exposed as an active electrode coupled with an indifferent electrode placed in the dorsum to deliver sympathetic stimulation on spinal T_5-L_4. Then, heparin 10 mg/kg, atropine 1 mg/kg and tubocurarine 1 mg/kg were injected iv. After the blood pressure was stabilized for 25 min, the pithed rats were stimulated with 30 V and 2 ms rectangular pulses and 0.1, 0.2, 0.5, 1, 2, 5, 10 Hz for 30 s at 3 min intervals. The frequency-pressor curves were drawn before and 15 min after melperone was given.

Rat isolated vas deferens Rats (262± SD 39 g) were killed by a blow on the head and exsanguination. The isolated vas deferens were placed in an organ bath containing Krebs-bicarbonate solution (containing propranolol 3.4 μmol/L) at 38℃ and gassed with 95% O_2 + 5% CO_2, loaded 1 g[7]. Field stimulation with single 30 V pulse, 0.5 ms duration was applied at 5 min intervals and drug was added 2 min after stimulation. The isometric tensions of the prostatic portion (250 ms after stimulation) and the epidydimal portion (650 ms after stimulation) were recorded with the tension transducer. Clonidine dose-tension inhibition curves of the prostatic portion and methoxamine dose-tension potentiation curves of the epidydimal portion were drawn before and 15 min after antagonists were added[7].

Melperone was synthesized and supplied by Department of Chemistry, Nanjing University. All drugs were dissolved in saline, except prazosin which was dissolved in 5% glucose solution. The pA_2 value was calculated with the Tallarida's method[8].

RESULTS

Blocking action of melperone on α-adrenoceptors Over a range of frequencies,

yohimbine 1 mg/kg and atenolol 1 mg/kg depressed the pressor responses elicited by electrical stimulation. Melperone 0.1 mg/kg depressed these responses further. After yohimbine (selective α_2-adrenoceptor blocker) was replaced with prazosin (selective α_1-adrenoceptor blocker) in the above case, pressor responses were also be depressed in similar extent by melperone in the same dose. Thus, melperone possessed the blocking actions on both α_1- and α_2-adrenoceptors (Fig 1).

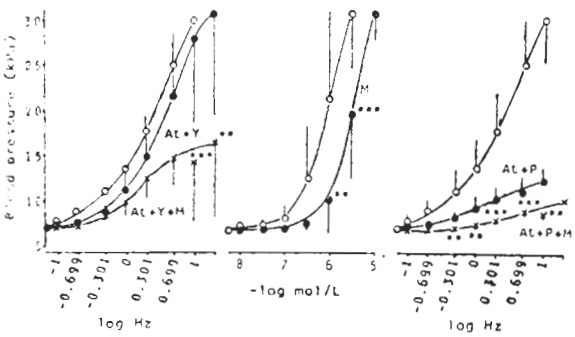


Fig 1. Effects on blood pressure by electrical stimulation of spinal cord (T_5-L_4) to bilaterally adrenalectomized pithed normotensive rats (A and C) and by methoxamine to normotensive rats (B). n = 6-9, $\bar{x}\pm$SD. *p>0.05, **p<0.05, ***p<0.01.
At: atenolol 1 mg/kg; M: melperone 0.1 mg/kg; P: prazosin 0.1 mg/kg; Y: yohimbine 1 mg/kg; (○) Pretreatment (-15 min) with saline.

Estimation of pA_2 and α_1/α_2 value of melperone In the isolated rat vas deferens, melperone made the methoxamine dose-tension potentiation curve and the clonidine dose-tension inhibition curve displaced rightward parallelly (Fig 2 & 3). The slopes were estimated as (m) = -1.18 and -1.05, and pA_2 = 9.33 and 6.14 respectively (Tab 1). Thus, α_1/α_2 selectivity ratio was estimated as 1542. The pA_2 (α_1), pA_2 (α_2), α_1/α_2 selectivity ratios of prazosin and yohimbine were also estimated as 9.77, 6.25, 3304 and 6.7, 8.35, 0.023 respectively.

DISCUSSION

Pithed rat preparation has been

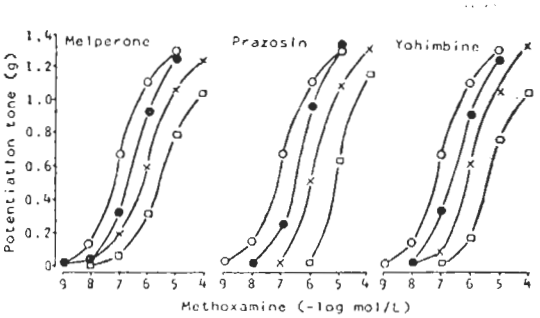


Fig 2. Potentiation of methoxamine in isometric tension response of epididymal portion of rat vas deferens to a single field stimulation (0.5 ms, 30 V). Pretreatment (-15 min) with normal saline (○), n = 14; melperone (-10 min, 1, 3, 10 μmol/L), n = 11; prazosin (0.3, 1.5, 8 μmol/L), n = 6; and yohimbine (0.3, 1.5, 7.5 μmol/L), n = 4.

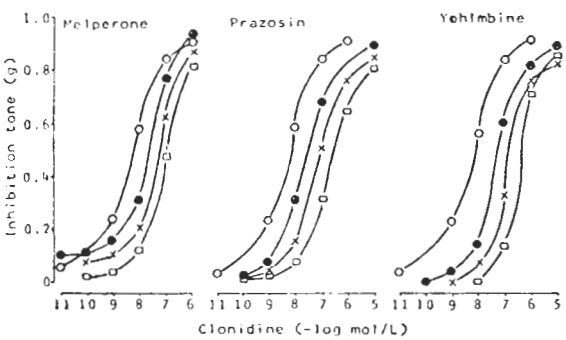


Fig 3. Inhibition of clonidine in isometric tension of prostatic portion of rat vas deferens to a single field stimulation (0.5 ms, 30 V). Pretreatment (-15 min) with normal saline (○), n = 14; melperone (-10 min, 2.3, 4.7, 9.5 μmol/L), n = 8; prazosine (2.5, 4.2, 6.3 μmol/L), n = 6; yohimbine (0.036, 0.063, 0.13 μmol/L), n = 6.

Tab 1. Selective ratio of melperone, prazosin and yohimbine on α-adrenoceptor subtypes

Antagonist	$pA_2(\alpha_1)$	$pA_2(\alpha_2)$	α_1/α_2
Melperone	9.33	6.14	1542
Prazosin	9.77	6.25	3304
Yohimbine	6.7	8.35	0.0225

regarded as a simplest and suitable model for differentiating the two types of α-adrenoceptors[9]. In present experiment, by using methoxamine as agonist, the competitive

antagonism of melperone on α_1-adrenoceptor was shown to be similar to that reported by other with different agonist[2]. Using the frequency-pressor response, melperone possessed also an antagonistic effect on intrasynaptic α_2-adrenoceptor, similar to that of yohimbine. Petersen didn't find the antagonism of melperone on presynaptic clonidine response, it might be related to the stimulating method employed by them, because lower frequency or continued stimulation might activate the negative feedback mechanism of transmitter release and thus might result in the attenuation of the effect of antagonist[10].

On the basis of our observation, the antagonism of melperone for the potentiation of methoxamine and the inhibition of clonidine in isolated rat vas deferens are all competitive, as the slopes were -1.18 and -1.05 respectively. The selectivity ratio of melperone is lower than that of prazosin, but the value of pA_2 (α_2, 6.14) of melperone is also lower than that of prazosin (6.25) and much lower than that of yohimbine (8.35).

Since melperone has neither β-blocking nor cholinergic effect[2], it still shows rather higher selectivity on α_1-adrenoceptor. The pA_2 and α_1/α_2 selectivity ratio of prazosin and yohimbine we obtained were slightly higher than that of other[11], as the different agonists were employed.

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美哌隆对α受体的选择性阻滞

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提要　用毁髓大鼠与大鼠离体输精管研究了美哌隆对α受体的选择性阻滞作用．与用同法测得的哌唑嗪的 α_1/α_2(3304)，育亨宾的 α_1/α_2(0.0225)相比，美哌隆的 α_1/α_2(1542)较哌唑嗪稍低，但其 pA_2(6.14)也较哌唑嗪(6.25)低，较育亨宾(8.35)低得更多．实验结果提示：美哌隆是一个类似于哌唑嗪，具有较高 α_1 受体阻滞作用的药物．

关键词　美哌隆；肾上腺素能α受体阻滞剂；毁髓大鼠；输精管；哌唑嗪

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