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 α1/α2 for adrenoceptor blockade of melperone, prazosin and yohimbine were estimated to be 1545, 3304 and 0.0225, respectively. The value of pA2 of melperone (6.74 ± 16.14) was lower than that of prazosin (6.25) and much lower than that of yohimbine (8.35). The results indicate that melperone is a

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drug with higher α1-adrenoceptor blocking action, comparable to prazosin.

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

Melperone is a neuroleptic, 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melperone did not induce the reflex tachycardia, but rather induced a bradycardia when the blood pressure decreased (unpublished data).

![Chemical structure of melperone]

Melperone possesses \( \alpha \)-adrenoceptor blocking action in pithed rats\(^{9,10} \). Taking the blood pressure elevation by clonidine in pithed rat as an index of postsynaptic \( \alpha \)-adrenoceptor excitation, and the heart rate slowing responding to sympathetic stimulation as an index of presynaptic \( \alpha \)-adrenoceptor excitation, Petersen\(^{11} \) evaluated the blocking action of melperone on pre- and post-synaptic adrenoceptors. However, the recent findings of postsynaptic \( \alpha \)-adrenoceptor mediated vasoconstriction make the analysis of \( \alpha \)-adrenoceptors more complicated. Both \( \alpha \)- and \( \alpha \)-adrenoceptor subtypes coexist at the sympathetic nerve endings, and both subtypes mediated vasoconstriction\(^{12} \) and could be excited by clonidine\(^{13} \). So, the estimation of the selectivity ratio of \( \alpha_1/\alpha_2 \) of melperone made by Petersen is unjustifiable and no precise ratio had been reported so far. Melperone may be a new type of potential anti-hypertensive drug and it is interesting to assess its \( \alpha_1/\alpha_2 \) selectivity ratio for exploring its therapeutic value and side effects.

**MATERIALS AND METHODS**

**Pithed rats** Normotensive rats (150 ± 50 g) under pentobarbital anesthesia and artificial respiration were pithed via the orbit\(^{9,11} \). After the blood pressure was stabilized, logarithmic accumulated 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 enamed wire rod with the tip exposed as an active electrode coupled with an indifferent electrode placed in the dorum to deliver sympathetic stimulation on spinal T\(_1\)-L\(_1\). Then, heparin 10 mg/kg, atropine 1 mg/kg, and tubocurarine 1 mg/kg were injected iv. After the blood pressure was stabilized for 20 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–pressure curves were drawn before and 15 min after melperone was given.

**Rat isolated vas deferens** Rats (263 ± 30 g) were killed by a blow on the head and exanguination. The isolated vas deferens were placed in an organ bath containing Krebs–bicarbonate solution (containing propanolol 3.4 μmol/L at 38°C and gassed with 95% O\(_2\) + 5% CO\(_2\) loaded 1 g/L). Field stimulation with single 50 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 epidiymal 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 epidiymal portion were drawn before and 15 min after antagonists were added\(^{14} \).

Melperone was synthesized and supplied by Department of Chemistry, Nanjing University. All drugs were dissolved in saline, except prazosin which was dissolved in 55% glucose solution. The pA\(_2\) value was calculated with the Tallarida's method\(^{14} \).

**RESULTS** Blocking action of melperone on \( \alpha \)-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 α₁-adrenoceptor blocker) was replaced with prazosin (selective α₁-adrenoceptor blocker) in the above case, pressor responses were also depressed in similar extent by melperone in the same dose. Thus, melperone possessed the blocking actions on both α₁- and α₂-adrenoceptors (Fig 1).

![Fig 1. Effects on blood pressure by electrical stimulation of spinal cord (Te-At) to bilaterally adrenalectomized phined normotensive rats (A and C) and by methoxamine to normotensive rats (B). n = 6–9. Y ± SD. *p < 0.05. **p < 0.01. A: atenolol 1 mg/kg; B: melperone 0.1 mg/kg; C: yohimbine 1 mg/kg; (C) Pretreatment (-15 min) with saline.]

Estimation of pA₂ and α₁/α₂ 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 pA₂ = 9.33 and 6.14 respectively (Tab 3). Thus, α₂/α₁ selectivity ratio was estimated as 15.42. The pA₂ (α₂), pA₂ (α₁), α₂/α₁ selectivity ratios of prazosin and yohimbine were also estimated as 9.77, 6.25, 3504 and 6.7, 6.25, 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, 50 V), Pretreatment (-15 min) with normal saline (○), n = 14: melperone (-10 min, 1.5, 10 μmol/L), n = 14: prazosin (0.3, 1.5, 5 μmol/L), n = 6: and yohimbine (0.5, 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, 2.5, 4.7, 9.5 μmol/L), n = 8: prazosin (2.5, 4.2, 8.5 μmol/L), n = 6: yohimbine (0.026, 0.065, 0.15 μmol/L), n = 6.]

**Tab 7. Selective ratio of melperone, prazosin and yohimbine on α-adrenoceptor subtypes**

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>pA₂(α₁)</th>
<th>pA₂(α₂)</th>
<th>α₂/α₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melperone</td>
<td>9.33</td>
<td>6.14</td>
<td>15.42</td>
</tr>
<tr>
<td>Prazosin</td>
<td>9.77</td>
<td>6.25</td>
<td>3504</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>6.7</td>
<td>6.25</td>
<td>0.023</td>
</tr>
</tbody>
</table>

regarded as a simplest and suitable model for differentiating the two types of α-adrenoceptors[17]. In present experiments, by using methoxamine as agonist, the competitive
antagonism of melperone on α₁-adrenoceptor was shown to be similar to that reported by other with different agonist[11]. Using the frequency–pressor response, melperone possessed also an antagonistic effect on intraneuronal α₁-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 antagonism[12].

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 pA₂(α₁, 6.14) of melperone is also lower than that of prazosin (6.75) and much lower than that of yohimbine (8.35).

Since melperone has neither β-blocking nor cholinergic effect[12], it still shows rather high selectivity on α₁-adrenoceptor. The pA₂ and α₁/α₂ 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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摘要：美哌隆的化学活性与α受体拮抗剂相似，研究了美哌隆对α受体的选择性阻滞作用，与司可巴胺的拮抗指数α1/α2（3.23±1.56），与α-甲基-α-酪胺（0.037±0.005）相比，美哌隆的拮抗指数α1/α2（15.42）远优于前者，但其α/β（6.24）也较哌替啶（4.23）高，较舒芬太尼（4.33）低。实验结果表明，美哌隆是一个类似酚酸类的α1受体阻滞剂，具有较高的α1受体拮抗作用的药物。

关键词：美哌隆，α受体拮抗剂，α/β比值，α1/α2比值。