The blocking effects of tolazoline and propranolol on axial movements of incisor teeth and on changes in arterial blood pressure induced by adrenaline in rats

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[Received on June 26, 1998; Accepted on August 3, 1998]

Key words: adrenaline/adrenergic blocker/tooth movement/rat incisor/blood pressure

Abstract: Axial tooth movements and arterial blood pressure were measured following intravenous injection of adrenaline, 1 hr before, and 1 and 2 hr after the injection of tolazoline (an α-adrenergic blocking agent) or propranolol (a β-adrenergic blocking agent). The initial increase in blood pressure induced by adrenaline was significantly suppressed and the successive decrease in blood pressure was markedly enhanced by pretreatment with tolazoline. In contrast to blood pressure changes, the initial extrusive tooth movement induced by adrenaline was not suppressed, and successive intrusive tooth movements induced by adrenaline were not potentiated, but suppressed. The initial increase in blood pressure induced by adrenaline was enhanced and the successive decrease in blood pressure was suppressed by pretreatment with propranolol. On the other hand, the initial extrusive tooth movement induced by adrenaline was not significantly potentiated, but successive intrusive tooth movements induced by adrenaline were markedly suppressed.

Pressure within the socket that may induce axial tooth movements might be regulated by various factors, such as resistance of the blood vessels, blood flow in the socket, and systemic arterial blood pressure, all of which are liable to change following an injection of adrenaline under the influence of α- or β-adrenergic blockers.
**Introduction**

Adrenaline induces a dose-dependent rapid extrusive movement of the rat incisor almost simultaneously with an increase in systemic arterial blood pressure, followed by intrusive tooth movement and a decrease in blood pressure. We previously suggested that extrusive tooth movement is primarily related to the rise in arterial blood pressure due to stimulation of vascular $\alpha$-adrenergic receptors and that stimulation of $\beta$-adrenergic receptors in the localized vasculature within the incisor socket causes a reduction in pressure and blood volume, followed by marked intrusive tooth movement.

Aars and Aars and Linden reported that sympathetic nerve stimulation induces intrusive tooth movement by altering blood pressure and volume in the periodontal ligament of the rabbit incisor and cat canine. They suggested that these responses are mediated by $\alpha$-adrenergic receptors because intrusive tooth movement is greatly reduced by injection of the $\alpha$-adrenergic blocking agent, phentolamine. Administration of noradrenaline, a potent stimulator of $\alpha$-adrenergic receptors, also induces intrusive tooth movements in the rabbit incisor and in the cat canine.

In addition, $\beta$-adrenergic antagonists induce a marked extrusion of the tooth. Aars suggested that a reduction in $\beta$-adrenergic tone leads to a rise in pressure and volume in the vessels within the periodontal ligament and, therefore, to extrusion of the rabbit incisor. Furthermore, subsequent injection of isoprenaline, a potent stimulator of $\beta$-adrenergic receptors, always induces rapid intrusions of the teeth. Nevertheless, the precise relationship between extrusive or intrusive tooth movements and stimulation or inhibition of vascular $\alpha$- and $\beta$-adrenergic receptors in continuously erupting incisors remains unclear.

The purposes of the present study were to investigate the effects of adrenaline on axial movements of the rat mandibular incisor and arterial blood pressure in rats pretreated with $\alpha$- or $\beta$-adrenergic blocking drugs, and to elucidate the relationship between tooth movement and adrenergic receptors.

**Materials and Methods**

1. **Animals**

Male Wistar rats ($n=20$), weighing 321 to 357 g at 10 to 13 weeks of age, were divided into two equal groups. They were immobilized by the method described previously. In brief, the rats were placed in a supine position and anesthetized via inhalation of 1.1% halothane in air through a tracheal tube connected to an artificial respirator at 100 strokes/min (3 ml/stroke). The lower margin of the jaw bone was surgically exposed and secured with a hemostat, which was affixed to the metal bar of a magnetic stand with acrylic resin. Each rat was administered atropine sulfate (25 mg) before the operation to prevent tracheal secretion. Rectal temperature was maintained at 35°C using a heating pad during the experimental period. A polyethylene tube was inserted into the left hind leg vein through which, drugs were administered to each rat at 1-hr intervals.

2. **Administration of drugs**

Two experiments were performed as follows.

**Experiment 1.** In one group of 10 rats, each animal was given an intravenous injection of 1 mg/kg body wt of tolazoline, a known $\alpha_1$- and $\alpha_2$-adrenergic receptor blocker (Imidaline, Yamanouchi Seiyaku Co., Tokyo). One hour before (control), and 1 and 2 hr after the injection of tolazoline, each animal was given intravenous injections of adrenaline (1 $\mu$g/kg) (Daiichi Seiyaku Co., Tokyo).

**Experiment 2.** In the other group of 10 rats, each animal was given an intravenous injection of 1 mg/kg body wt of tolazoline, a known $\alpha_1$- and $\alpha_2$-adrenergic receptor blocker (Imidaline, Yamanouchi Seiyaku Co., Tokyo). One hour before (control), and 1 and 2 hr after the injection of tolazoline, each animal was given intravenous injections of adrenaline (1 $\mu$g/kg) (Daiichi Seiyaku Co., Tokyo).
3. Axial movements of the incisor
Axial movement of the left mandibular incisor was measured by a non-contacting displacement detector; that is, the movement of a thin metal plate attached to the tooth surface was recorded. Data was fed into a computer (PC-9801DA; NEC, Tokyo) at 1-sec intervals. The values recorded by the detector were corrected for the curvature of the incisor and the radial distance between the tooth surface and the metal plate.

4. Arterial blood pressure
Arterial blood pressure was measured using a pressure transducer (MP-15, Micron Instruments, CA, U. S. A.) that is, a polyethylene tube was inserted into the mid-tail artery and through which, the pressure was recorded. The arterial blood pressure was fed into a computer (PC-9801DA; NEC, Tokyo) at 1-sec intervals during the experimental period.

5. Maximum tooth movement and blood pressure change
Tooth positions at the maximum extrusive movement (peak point), maximum intrusive movement (bottom point), and recovery (recovery point), and arterial blood pressures at the maximum increase (peak point), maximum decrease (bottom point), and recovery (recovery point) were examined following injections of adrenaline before and after an injection of tolazoline or propranolol.

6. Statistical analysis
Differences of the mean values were compared by Scheffe’s method for multiple comparisons after analysis of variance (ANOVA).

![Fig. 1](image-url)

Fig. 1 Records of tooth displacement (upper column) and arterial blood pressure (lower column) following the injection of adrenaline, 1 hr before (control), and 1 and 2 hr after the injection of tolazoline (α-adrenergic blocking agent). Points (arrow heads) a, b, and c indicate peak, bottom, and recovery of the tooth displacement, respectively; points a', b', and c', indicate peak, bottom, and recovery of the arterial blood pressure, respectively. Arrows indicate the time of drug injection (designated as 0 min). Each curve was obtained from combined values for ten animals.
Results

1. Effects of tolazoline on tooth displacement and changes in arterial blood pressure induced by adrenaline

Figure 1 shows records of tooth displacement and arterial blood pressure following the injection of adrenaline, 1 hr before (control), and 1 and 2 hr after the injection of tolazoline. Before the injection of tolazoline, adrenaline induced an initial extrusive movement of the incisor and an increase in arterial blood pressure. Then, a marked intrusive tooth movement and a decrease in arterial blood pressure occurred. One hour after the injection of tolazoline, the initial extrusive tooth movement by adrenaline appeared to be slightly enhanced, however, successive intrusive movement was obviously suppressed. At 2 hr, the extrusive tooth movement was similar to that at 1 hr, and the intrusive tooth movement was slightly greater than that at 1 hr, indicating recovery from the suppressive effect of tolazoline. After the injection of tolazoline, the initial increase in arterial blood pressure by adrenaline was markedly suppressed, but a successive decrease in blood pressure was markedly enhanced both at 1 and 2 hr.

2. Effects of propranolol on tooth displacement and changes in arterial blood pressure induced by adrenaline

Figure 2 shows records of tooth displacement and arterial blood pressure following the injection of adrenaline, 1 hr before (control), and 1 and 2 hr after the injection of propranolol. Effects of adrenaline on tooth movement, and on arterial blood pressure were similar before the injection of α- and β-adrenergic blockers (control). One hour after the injection of propranolol, the initial extrusive tooth movement by adrenaline appeared to be similar to that of the control but a successive intrusive tooth movement was markedly suppressed. At 2 hr, the extrusive tooth movement was similar to that at 1 hr, and the intrusive tooth movement was greater than that at 1 hr, indicating recovery from the suppressive effect of propranolol.
movement was slightly greater than that at 1 hr, indicating recovery from the suppressive effect of propranolol. After the injection of propranolol, an initial increase in arterial blood pressure by adrenaline was obviously enhanced, however, successive decrease in blood pressure was markedly suppressed at both 1 and 2 hr.

3. Changes in tooth displacement and arterial blood pressure following injection of tolazoline or propranolol alone

Figure 3 shows changes in tooth displacement and arterial blood pressure following the injection of tolazoline or propranolol alone; the observation was performed for approximately 40 min. Following the injection of tolazoline, a slight extrusive tooth movement (2.1 μm; the mean value is shown in parentheses hereafter) was observed followed by a gentle intrusive tooth movement (−6.9 μm); the position of the tooth returned to the initial level within approximately 40 min. Arterial blood pressure decreased immediately (−25.7 mmHg), and returned to the initial level within approximately 10 min. Following the injection of propranolol, a very slight and temporal intrusive tooth movement (−1.3 μm) was observed, followed by a continuous extrusive tooth movement. Arterial blood pressure decreased slightly and temporarily (−19.8 mmHg), and remained almost constant at a slightly lower level thereafter.

4. α- or β-adrenergic blocking effects on maximum tooth displacement

Effects of pretreatment with α- or β-adrenergic blocking agents on maximum tooth displacement induced by adrenaline are shown in Figure 4. Control values were not significantly different between the tolazoline- and propranolol-injected groups. Pretreatment with either tolazoline or propranolol had no significant effect on the initial extrusive movement of the incisor at 1 and 2 hr after the injection. On the other hand, the maximum intrusive tooth movement
induced by adrenaline after pretreatment with tolazoline was significantly less than the control value ($p<0.01$, Scheffe's method) at 1 hr but not at 2 hr. The maximum intrusive tooth movements induced by adrenaline were markedly suppressed ($p<0.001$, Scheffe's method) at 1 and 2 hr after pretreatment with propranolol.

5. $\alpha$-or $\beta$-adrenergic blocking effects on arterial blood pressure

Effects of pretreatment with $\alpha$- or $\beta$-adrenergic blocking agents on adrenaline-induced changes in arterial blood pressure are shown in Figure 5. The maximum increases in arterial blood pressure were markedly suppressed at 1 and 2 hr ($p<0.001$, Scheffe's method) and the maximum decreases in blood pressure were significantly enhanced at 1 and 2 hr ($p<0.01$ and $p<0.001$, Scheffe's method, respectively) after pretreatment with tolazoline. On the other hand, the maximum increases in arterial blood pressure induced by adrenaline were significantly enhanced at 1 and 2 hr ($p<0.001$, Scheffe's method) after pretreatment with propranolol and the maximum decreases in blood pressure were markedly suppressed at 1 and 2 hr ($p<0.001$, Scheffe's method).

Discussion

In the present experiment, the doses of tolazoline, propranolol, and adrenaline were determined according to previous reports on experimental animals such as dogs, piglets, rabbits, and rats and our preliminary observations (unpublished data). The time between administration of $\alpha$- or $\beta$-adrenergic blockers and adrenaline was also determined according to our preliminary observations, when arterial blood pressure and tooth movement appeared to have recovered from the single effects of $\alpha$- or $\beta$-adrenergic blockers (Fig. 3). Thus, the doses of tolazoline, propranolol, and adrenaline, and the time intervals between administration of the blockers and adrenaline were appropriate in the present study.

There have been several reports that tolazoline decreases systemic arterial blood pressure. Blockade of $\alpha_1$-adrenergic receptors inhibits vasoconstriction induced by endogenous catecholamines; vasodilatation may occur in both arteriolar resistance vessels and veins resulting in a fall in blood pressure because of decreased peripheral vascular resistance. In the present study, an immediate and temporal decrease in arterial blood pressure was observed after the injection of tolazoline alone (Fig. 3), due perhaps to the blockade of $\alpha$-adrenergic receptors and reduction of the peripheral resistance. Decrease in vascular resistance within the socket may reduce internal pressure within the socket, thereby inducing gentle intrusive tooth movement (Fig. 3).

Tolazoline effectively blocks the pressor action of adrenaline in experimental animals and this effect is produced by blocking the peripheral vasoconsticting action of adrenaline. When $\alpha$-adrenergic receptors are blocked by tolazoline, excess adrenaline acts on the $\beta$-adrenergic receptors and potentiates the fall in blood pressure. In the present study, an initial adrenaline-induced increase in arterial blood pressure was effectively suppressed and a successive decrease in blood pressure was markedly enhanced by pretrat-
ment with tolazoline, as expected (Figs 1 and 5).

In contrast to blood pressure changes, the initial extrusive tooth movement induced by adrenaline was not suppressed by pretreatment with tolazoline (Figs 1 and 4). Pretreatment with tolazoline causes a decrease in peripheral vascular resistance and an increase in blood flow. In the present experiment, immediately after the injection of adrenaline, we observed a very slight and temporal increase in systemic arterial blood pressure (Figs 1 and 5), indicating an imperfect blockade of vascular \( \alpha \)-receptors. It is possible that such a slight increase in arterial blood pressure can cause a marked increase in pressure within the socket, particularly when blood flow is increased by potentiation of cardiac \( \beta \)-receptors and vascular \( \beta \)-receptors, resulting in the extrusive movement of the incisor.

Although blood pressure decreased markedly, the successive adrenaline-induced intrusive tooth movement was not potentiated but rather suppressed in rats pretreated with tolazoline (Figs 1 and 4). It is possible that the intrusive tooth movement was not potentiated by the \( \alpha \)-adrenergic blocker due to the following reasons. Following the injection of adrenaline, the pressure in the socket in rats pretreated with tolazoline did not fall as much as that in the control. It is suggested that the low compliant environment in the socket did not allow further dilatation of the vasculature, because the blood vessels in the socket had already been sufficiently relaxed by the \( \alpha \)-adrenergic blocking action of tolazoline. We have no direct evidence, however, supporting this hypothesis. The pressure within the socket could be regulated by various factors such as the resistance of blood vessels, blood flow in the socket, and systemic arterial blood pressure, all of which are liable to change following the injection of adrenaline under influence of adrenergic blockers.

After the injection of propranolol alone, a temporal decrease in blood pressure was observed (Fig. 3), consistent with previous reports. Propranolol decreases cardiac output due to blockade of cardiac \( \beta \)-receptors and increases peripheral resistance due to blockade of vascular \( \beta \)-receptors. Because it has been reported that propranolol initially causes a transient vasodilatation and then subsequent sustained vasoconstriction, it is possible that a decrease of cardiac output and initial transient vasodilatation by the drug causes a temporal decrease of blood pressure. An almost immediate increase of extrusive tooth movement, however, was observed following the injection of propranolol alone (Fig. 3). Aars has reported that propranolol induced a marked extrusion of the rabbit incisor, probably due to reduced vasodilator tone (or increased vasoconstrictor tone) in periodontal postcapillary blood vessels. If an increase of pressure within the socket was rapid and predominant to a temporal decrease of blood pressure, an almost immediate extrusive tooth movement in the rat incisor would occur.

Propranolol augments the pressor response to adrenaline. In the present study, the initial increase in systemic arterial blood pressure induced by adrenaline was enhanced and the successive decrease in blood pressure was suppressed by pretreatment with propranolol (Figs 2 and 5). These results indicate that the pressor action of adrenaline due to stimulation of \( \alpha \)-adrenergic receptors was potentiated and the depressor action due to stimulation of \( \beta \)-adrenergic receptors was blocked by propranolol in our experiments.

The initial extrusive tooth movement induced by adrenaline was not significantly potentiated by pretreatment with propranolol (Figs 2 and 4). Following the injection of adrenaline, the pressure in the socket in rats pretreated with propranolol did not rise significantly as compared with control rats, probably because the vascular tone in the socket had been increased by the \( \beta \)-blocking action of propranolol before the injection of adrenaline. We do not have any evidence, however, supporting this hypothesis. The successive intrusive tooth movement induced by adrenaline was markedly suppressed by pretreatment with propranolol. This result supports the view that intrusive tooth movement is closely related to the stimulation of \( \beta \)-adrenergic receptors, as suggested by previous investigators.
Acknowledgements

We express our sincere gratitude to Professor M. Chiba, Department of Pharmacology, Tsurumi University for his continuous guidance and encouragement. We also express our appreciation to Professor K. Seto, First Department of Oral and Maxillofacial Surgery, and Professor Y. Amemiya, Department of Dental Anesthesiology, Tsurumi University.

References


