Pre- and Postsynaptic $\alpha$-Adrenergic Receptor Effects of Trazodone in the Anesthetized Dog

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ABSTRACT


The $\alpha$-adrenergic blocking properties of trazodone were assessed in spinal-sectioned, vagotomized dogs. Both the inhibition by clonidine of the tachycardia produced by continuous cardiac accelerator nerve stimulation (presynaptic effect) and the vasopressor effects of clonidine (postsynaptic effect) were antagonized by trazodone and phentolamine in this model. The results indicate that although it is 12–18 times less potent on a weight basis, trazodone, like phentolamine, blocks presynaptic $\alpha$-adrenergic receptors on the cardiac nerves of anesthetized dogs. Trazodone, unlike imipramine, did not potentiate the positive inotropic responses elicited by exogenously administered norepinephrine. The latter observation supports the interpretation that trazodone altered positive chronotropic responses to cardiac accelerator nerve stimulation via presynaptic $\alpha$-receptor blockade rather than by either an interference with neuronal reuptake of norepinephrine or a heightening of $\beta$-adrenergic receptor sensitivity.

Key words: trazodone, presynaptic actions, postsynaptic effects, $\alpha$-receptor blockade

INTRODUCTION

Trazodone is a chemically novel and clinically efficacious antidepressant agent possessing a spectrum of activities not resembling that of other psychotropic agents. Unlike the tricyclics, trazodone lacks antiserpine activity, does not potentiate catecholamines, is neither a monoamine oxidase inhibitor nor an anticholinergic agent, but does inhibit re-uptake of 5-HT into serotonergic neurones and does block $\alpha$-adrenergic receptors peripherally [see Al-Yassiri et al., 1981].

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postsynaptic α-receptor blocking properties of trazodone on noradrenergic nerves have been demonstrated via its ability to attenuate (a) agonist pressor responses in rats [Silvestrini et al., 1968], cats [Silvestrini et al., 1968], and dogs [Boissier et al., 1974; Gomoll et al., 1979]; (b) nictitating membrane tension changes in cats [Silvestrini et al., 1968; Boissier et al., 1974]; and agonist-elicited contractile response of (c) isolated rabbit ear artery [Boissier et al., 1974]; and (d) guinea pig seminal vesicle [Boissier et al., 1974] preparations in vitro. This postsynaptic antagonist property of trazodone has been proposed to be, at least in part, responsible for the lowering of blood pressure recorded in the intact, anesthetized dog [Gomoll et al., 1979].

The role, if any, which presynaptic α-receptor actions of trazodone play in the overall pharmacologic response has not been investigated. An attempt to characterize an action at this site is of interest because the release of norepinephrine from sympathetic nerve terminals has been shown to be regulated by presynaptic α-adrenoreceptors [Starke and Endo, 1976]. Activation of these receptors by α-adrenergic agonists (including norepinephrine) has been shown to suppress the release of additional transmitter, while their blockade augments transmitter release [Starke and Endo, 1976; Langer, 1974].

The present investigation was undertaken to explore the possible influence of trazodone on presynaptic regulatory mechanisms as they relate to alterations in sympathetic transmission to the heart and/or the control of heart rate. The capacity of an agent to reverse the inhibitory effects of clonidine on the tachycardia produced by cardiac accelerator nerve stimulation and to antagonize the vasopressor effects of clonidine were utilized, respectively, to compare the presynaptic and postsynaptic effects [Constantine et al., 1978] of trazodone relative to those of phentolamine in the anesthetized dog. This report describes the results of that comparison.

METHODS

Adult, random-source dogs of either sex and of body weights between 9.3 and 17.3 kg were anesthetized with pentobarbital sodium (30 mg/kg) or a combination of pentobarbital sodium (15 mg/kg)–barbital sodium (225 mg/kg) given intravenously. A tracheotomy was performed and the animals were ventilated with room air at a rate of 22/min and tidal volume of 20 ml/kg with a respirator (Harvard). Systemic arterial blood pressure was recorded from the thoracic aorta via a cannula in the left carotid artery using a Statham (P23Db) transducer. Heart rate was interpreted from the arterial pulse pressure or by means of tachometer. All measured variables were recorded on a Sanborn (Model 350) optical recording polygraph.

The data were statistically analyzed using the Student t-test for paired observations; a P value of < .05 indicated a level of significant change.

Continuous Cardiac Accelerator Nerve Stimulation (n = 16, average weight 12.8 kg, pentobarbital anesthesia)

Dogs in this series of studies were bilaterally vagotomized and subjected to spinal cord transection at the second cervical segment. The chest was opened via a midsternal thoracotomy, and the right cardiac accelerator nerve was exposed, isolated from the stellate ganglion, and prepared for bipolar electrical stimulation (Grass S8). Upon completion of the surgical procedures, a 30 to 60-min interval was allowed for blood pressure and heart rate to stabilize. Heart rate was then increased by continuous cardiac accelerator nerve stimulation (12-V intensity, 2-msec pulse duration, 1-Hz frequency). When heart rate became stable (5–8 min), 20 µg/kg clonidine was injected intravenously over a 15-sec interval. This was followed within 5–7 min by increasing intravenous doses of either trazodone HCl (0.1, 0.3, 1, 3 mg/kg) or phentolamine mesylate (10, 50, 250, 1250 µg/kg). A 2- to 3-min interval was allowed to elapse between the successive doses of trazodone or phentolamine. Four dogs subjected to clonidine injection and given solvent (0.9% saline) only at appropriate times during continuous nerve stimulation rather than an antagonist drug served as controls for this model.
Postsynaptic $\alpha$-Adrenergic Blocking Properties ($n = 7$, average weight 15.0 kg, pentobarbital–barbital anesthesia)

In these experiments, the heart was exposed via a midsternal thoracotomy and supported in a pericardial cradle. Alterations in contractile force were measured employing a Walton-Brodie strain gauge arch sutured onto the epicardial surface of the right ventricle. Upon completion of surgery and stabilization of the measured variables, the vasopressor and positive inotropic responses produced by norepinephrine (0.03, 0.1, 0.3 $\mu$g/kg) were recorded. In separate groups of four and three dogs, increasing doses of trazodone HCl (1.3, 10 mg/kg) or imipramine HCl (0.5, 1.5, 5 mg/kg) respectively, were injected intravenously over a 1-min interval. Ten minutes following administration of each dose of either drug, the responses to a repeat series of norepinephrine injections were recorded. An interval of 30 min was allowed to elapse between the administration of each successive dose of trazodone or imipramine.

Drugs

All drug dosages refer to the base of the respective test agent and were given in 0.9% saline solution via a cannula placed in a branch of the right femoral vein.

RESULTS

Effects on Clonidine Responses In the Presence of Continuous Cardiac Accelerator Nerve Stimulation

The mean basal heart rate was 102 bpm in the 12 vagotomized, spinal-sectioned dogs used for drug study. Continuous cardiac accelerator nerve stimulation induced sustained increases in heart rate of 43–110 bpm (mean = 68 bpm) ($P < .001$ vs control). Intravenous administration of clonidine slowed this rate by an average of 37 bpm (range = 13–93 bpm) ($P < .01$).

Both trazodone (0.1, 0.3, 1, 3 mg/kg) and phentolamine (10, 50, 250, 1250 $\mu$g/kg) in separate groups of six dogs each caused a dose-related antagonism of the inhibitory effect of clonidine on heart rate. Results from regression analyses of these dose-response data are shown in Figure 1A. The cumulative dosages of trazodone or phentolamine producing 50% inhibition of the clonidine-induced bradycardia were 0.62 and 0.034 mg/kg, respectively.

Mean arterial pressure was increased by 97 mm Hg (range 63–128 mm Hg) or from a mean basal level of 65 to 165 mm Hg ($P < .001$) following the injection of clonidine during continuous cardiac nerve stimulation. Administration of trazodone or phentolamine resulted in dose-related inhibition of this hypertensive response. Interpretations from regression analyses of dose-response data indicated that the mean cumulative dose of trazodone producing 50% inhibition of this pressor response was 0.86 mg/kg; that for phentolamine was 0.069 mg/kg (Fig. 1B).

In the series of four control dogs, accelerator nerve stimulation elevated heart rate 64 bpm; clonidine administration lowered rate 34 bpm, and there was no change for the next 19 min. Mean arterial blood pressure in these same dogs was 63 mm Hg before and 172 mm Hg after clonidine injection. Blood pressure gradually fell during the ensuing 19-min observation interval; however, the maximum mean recovery never exceeded 24 ± 4%.

Effects on Norepinephrine-Induced Pressor and Inotropic Responses

Intravenous doses of trazodone (1, 3, 10 mg/kg) produced dose-related antagonism of the diastolic pressor responses produced by norepinephrine (Fig. 2A). As indicated, there was a shift in the dose–response curves to the right and down as trazodone dosage increased. In the presence of imipramine (a tricyclic antidepressant known to interfere with catecholamine re-uptake) the $\alpha$-receptor-mediated norepinephrine pressor responses were significantly ($P < .05$) potentiated, rather than blocked, following agonist challenge doses of 0.1 and 0.3 $\mu$g/kg (Fig. 2B).
Fig. 1. Regression plots for antagonism by trazodone (◇) or phentolamine (●) of clonidine-induced (A) inhibition of tachycardia produced by continuous cardiac accelerator nerve stimulation and (B) elevation of arterial blood pressure in vagotomized, spinal-sectioned dogs. Cumulative doses of trazodone and phentolamine are plotted on abscissa; percentage antagonism of bradycardia or pressor response caused by clonidine is shown on ordinate. Numbers of dogs studied, computed regression equations, correlation coefficients, and interpreted ED50 values are indicated.
Fig. 2. Dose–response regression lines for the effects of (A) trazodone and (B) imipramine on the rise in diastolic blood pressure elicited by iv. norepinephrine in anesthetized dogs (N = 4 & 3, respectively). Mean responses and SEM (vertical bars) to each of three doses of norepinephrine are shown prior to (control) and after iv. administration of 1, 3, and 10 mg/kg trazodone or 0.5, 1.5, and 5 mg/kg imipramine. Asterisk indicates level of significant difference from control (paired Student t-test): *P < .05; **P < .01.
The β-receptor-mediated positive inotropic responses elicited by norepinephrine were not significantly altered by administration of trazodone in doses up to 10 mg/kg (Fig. 3A). In the presence of increasing doses of imipramine, however, the contractile force responses to norepinephrine were significantly enhanced (Fig. 3B).

**DISCUSSION**

While the fall in arterial pressure recorded following trazodone in anesthetized dogs has been ascribed, at least in part, to the α-adrenergic blocking properties of this agent rather than to a direct vasodilator effect [Gomoll et al., 1979], an explanation for the simultaneous slowing of heart rate which was observed has not been established. This fall in heart rate does not appear to be the result of either β-adrenergic withdrawal or cholinergic activation because the response is obtained not only in intact, anesthetized dogs [Gomoll et al., 1979] but also in catecholamine-depleted [Gomoll, unpublished observations] and/or atropine-pretreated [Gomoll et al., 1979] animals.

In the intact, anesthetized dog, presynaptic α-receptor antagonists such as phentolamine have been shown to augment norepinephrine release and to enhance the positive chronotropic response evoked by cardiac nerve stimulation [Constantine et al., 1978]. The α-receptor agonist clonidine, in contrast, has been shown to cause a decreased release of transmitter from sympathetic nerve endings as the result of its concurrent prejunctional inhibition of α-adrenoceptors [Starke and Altmann, 1973]. It is by virtue of this presynaptic action that clonidine is capable of inhibiting the tachycardia produced by electrical stimulation of the cardiac sympathetic nerves [Scriabine and Stavorski, 1973], and this can be reversed by concurrent administration of phentolamine [Constantine et al., 1978].

In the present study, trazodone antagonized both the inhibitory effect of clonidine on heart rate responses to cardiac accelerator nerve stimulation and the peripheral vasopressor effects of clonidine. Even though trazodone was 12–18 times less potent on a weight basis than phentolamine,
its profile of action was analogous under the same experimental conditions. These observations indicate that trazodone blocks presynaptic $\alpha$-receptors on the cardiac accelerator nerve as well as postsynaptic $\alpha$-receptors in the vascular bed. Although a reduced re-uptake of norepinephrine and/or an increased sensitivity of $\beta$-receptors to neurotransmitters could also be responsible for the positive chronotropic effects of trazodone in the presence of clonidine, neither possibility appears likely, based upon the failure of trazodone to alter the positive inotropic responses to exogenously administered norepinephrine (Fig. 3A). Verification of this interpreted lack of effect of trazodone on catecholamine uptake would, of course, require other in vivo or in vitro studies in which uptake was measured directly. Potentiation of $\alpha$- as well as $\beta$-adrenergic responses via a known capacity to block re-uptake of norepinephrine, however, can be demonstrated following imipramine (Figs. 2B, 3B).

Comparison of the ED$_{50}$ values for trazodone and phentolamine, as antagonists of clonidine actions on the cardiac accelerator nerve (a presynaptic effect) with their corresponding values for antagonism of clonidine-induced hypertension (a postsynaptic effect), indicates that trazodone is essentially equiactive at both sites, whereas phentolamine appears to be at least two times more potent at pre- than at the postsynaptic receptors. Extensions of the present findings into clinical situations, however, should be approached with caution not only because of the species differences but also because of known variances in noradrenergic nerves on different organs of the same species [Constantine et al., 1978]. The mechanism responsible for the heart rate slowing effect of trazodone in the anesthetized dog remains unresolved especially in view of the present failure to demonstrate any presynaptic agonist action for the drug. Other mechanisms which might be involved, and would require further investigation, include actions of the drug on central and/or peripheral serotonergic [Blatt et al., 1979], dopaminergic [Lokhandwala et al., 1979], or purinergic [Irvin et al., 1979] pathways.

REFERENCES