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PERIVASCULAR ACTION OF THE LOCAL ANAESTHETIC, LIDOCAINE, ON PIAL TERMINAL ARTERIOLES: DIRECT OBSERVATIONS ON THE MICROCIRCULATION

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Considerable controversy currently exists with respect to whether or not local anaesthetics exert direct action on cerebral arteriolar tone. *In situ* experiments were therefore undertaken on pial terminal arterioles of rats to determine whether or not perivascular application of lidocaine exerts any action on such cerebral vessels. Vessel size was assessed with an image-splitting television microscope recording system. The vessels studied ranged in size from 25 to 30 μm. Lidocaine was applied in artificial CSF in dosages of 0.01, 0.1, 1.0 and 2.0 mg. Significant dose-dependent dilatation (i.e., 15.7–45.3% increases in lumen sizes) of the pial terminal arterioles was observed. The results are discussed in light of current developments concerning the mechanism whereby local anaesthetics alleviate increased intracranial pressure and cerebral vasospasm.

Introduction Although most investigations, involving both animal models and man, that deal with cerebral blood flow, cerebral ischaemia and intracranial hypertension have focused on large calibre blood vessels, smaller conduits in the microcirculation are known to play important roles in these events. Terminal resistance (arteriolar) vessels in the brain proper, as well as the pial vasculature, contribute to the maintenance of cerebral autoregulation and respond abruptly to physico-chemical changes in their extravascular milieu (Kuschinsky & Wahl, 1978; Mchedlishvilli, 1980; Siesjö, Berntman & Nilsson, 1980). However, little in the way of precise, direct quantitative *in situ* information is available in relation to the effects that anaesthetics and local anaesthetics exert on these terminal pial arterioles.

One recent clinical trial (Bedford, Persing, Pobereskin & Butler, 1980) maintains that the intravenous local anaesthetic, lidocaine, may be efficacious in reducing increased intracranial pressure in patients with space-occupying lesions at the time of surgery. The mechanism of such action is unknown; the effect(s) of local anaesthetics on cerebral metabolism and circulation has not, as yet, been investigated extensively (Altura & Altura, 1974; Sakabe, Maekawa, Ishikawa & Takeshita, 1974; Bedford *et al.*, 1980).

One of us has demonstrated, previously, using high-resolution *in vivo* microscopy, that a variety of local anaesthetics, including lidocaine, can exert direct vasodilator effects on terminal arterioles in the intestinal and skeletal muscle microvasculatures (Altura, 1967; 1971; 1978; Altura & Altura, 1974). To our knowledge, comparable direct *in situ* microscopic data are not available for cerebral (or pial) terminal arterioles. We now show that perivascular application of lidocaine to rat pial terminal arterioles exerts dose-dependent potent vasodilator actions on these important resistance vessels.

Methods Seven male Wistar rats, ranging in weight from 126–210 g, were lightly anaesthetized with intramuscular pentobarbitone sodium (Nembutal, 25 mg/kg). After induction of anaesthesia, tracheostomies were performed and catheters were placed in femoral arteries and veins for measurement of arterial blood gas (Po_2, Pco_2), pH and infusion of additional anaesthesia or drugs, respectively. A right parietal-temporal craniotomy was performed by scraping the cranium with a scalpel down to the dura, by a method similar to that described previously (Altura, Gebrewold & Lassoff, 1980; Lassoff & Altura, 1980); the dura was then incised and stripped. Artificial cerebral spinal fluid (CSF) (composition in meq/1: Na^+ 155, Cl^- 137, HCO_3^- 21, K^+ 3.5, Mg^{2+} 1.3, Ca^{2+} 2.2 and glucose 6), maintained at a temperature between 36 and 37.5°C and at a pH of 7.3 to 7.4, was allowed to drip on to the exposed brain surface. The brain surface temperature was kept close to 37.5°C and measured with a thermistor probe.

Pial arteriolar diameters (25 to 30 μm o.d.) were examined and measured quantitatively (up to 3000 ×) with an image-splitting television microscope recording system, similar to that described previously for microvessels (Altura, 1975). The reactivity of selected terminal arterioles was tested before, and after, lidocaine HCl, by local application of 0.1 ml of a 50 mg/ml $BaCl_2$ solution. Pial arterioles that failed to yield a 30 to 40% constriction in response to the standard dose of barium were not used in this study. $BaCl_2$ has been shown to produce consistent and reproducible constrictor responses on

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normal rat pial arterioles (Altura *et al.*, 1980; Lassoff & Altura, 1980). Lidocaine HCl (dissolved in artificial CSF) was applied locally (0.1, 1.0, 10.0 and 20.0 mg/ml solutions) to the vessels in volumes of 0.1 ml. Periodically throughout the experiments, drug-free artificial CSF in 0.1 volumes was also tested for vasoactivity. Reapplication of the test dose of $BaCl_2$, at the end of the experiments, insured that the pial arterioles had been reactive throughout the testing of lidocaine.

Between drug application, the exposed brain surface was washed with artificial CSF for 12–15 min or until the vessels returned to control size. Systolic blood pressure was measured continuously in selected animals (average mean = 122 mmHg). At selected intervals throughout the experiments arterial blood samples were obtained for measurements of pH, P_{O_2} and P_{CO_2} and the mean values obtained were 7.39, 92 mmHg and 30.2 mmHg (Dittmer, 1961) respectively. Paired *t* tests were used for statistical analysis of the differences between mean values (± s.e.mean) before and after $BaCl_2$ and lidocaine application.

Results Perivascular application of 0.1 ml artificial CSF had no significant effect on the diameters of the pial arterioles. Table 1 indicates that increasing doses of lidocaine HCl significantly increased the vessel calibres by 15 to 45%. The vasodilator action of perivascularly applied lidocaine persisted in each terminal arteriole for between 3 and 4 min. Concomitant with the arteriolar dilator action, we observed increased, rapid capillary blood flow. Application of $BaCl_2$ (50 mg/ml) at the beginning and end of the experiments resulted in the expected significant decreases (30–45%) in vessel calibre (Altura *et al.*, 1980; Lassoff & Altura, 1980). Values for the paired *t* test were statistically significant for all values, with a *P* value < 0.0001 in all cases.

Discussion The major effect of lidocaine on the circulation is to induce peripheral vasodilatation, although it has been shown to produce constriction of lobar venous vessels of the lung in the intact dog (Altura & Altura, 1974). The latter appears to be an indirect effect brought about by lidocaine potentiating the action of catecholamines on vascular smooth muscle. *In vitro*, lidocaine can induce contraction of cat and rat mesenteric venous smooth muscle that is not only concentration-, but tone-dependent (Altura & Altura, 1974). Moreover, local anaesthetics in high concentrations ($> 10^{-5}$ M) can inhibit drug-induced contractions of isolated peripheral arterial and venous vessels. Earlier studies indicate that lidocaine is able to relax drug- and hormone-induced contractions of peripheral blood vessels, both *in vivo* and *in vitro*, at concentrations equal to, or greater than, 0.5 μg/ml (Altura & Altura, 1974).

There is a paucity of knowledge concerning the precise effects that local anaesthetics exert on cerebral blood flow and metabolism. In one previous study (Scheinberg, Jayne & Blackburn, 1952), intravenous administration of procaine to human subjects failed to produce any significant change in the cerebral metabolic rate for oxygen uptake, but did increase cerebral vascular resistance. It should be pointed out that lidocaine crosses the blood-brain barrier with relative ease (Sakabe *et al.*, 1974). When given in low dosages, lidocaine has been shown to depress the cerebral metabolic rate of oxygen uptake ($CMRO_2$) in dogs, whereas when a concentration capable of inducing seizures was infused at a constant rate, the $CMRO_2$ increased dramatically (Sakabe *et al.*, 1974). The authors of this study concluded that a non-seizure producing dose of lidocaine depresses cerebral respiration, while higher doses, which induce seizures, increase respiration.

In view of the fact that little is known about the action of lidocaine on cerebral blood vessels, the present direct *in situ* microcirculatory study is of

Table 1 Responsiveness of rat pial arterioles to local perivascular application of lidocaine hydrochloride

Test agonist	*Dose* (mg/ml)	*Control diameter size* (μm)	*Diameter size after agonist* (μm)	*% change*
$BaCl_2$ (initial)	50.0	29.1 ± 1.26*	17.5 ± 1.33†	−39.8‡
Lidocaine	0.1	28.6 ± 1.12	33.1 ± 1.48†	+15.7
	1.0	28.9 ± 1.00	37.8 ± 1.38†	+30.8
	10.0	29.0 ± 0.94	40.6 ± 1.58†	+40.0
	20.0	29.4 ± 0.89	42.7 ± 1.78†	+45.3
$BaCl_2$ (final)	50.0	29.4 ± 0.89	18.1 ± 0.82†^{NS}	−38.4

*Values are given as means ± s.e.mean; $n = 7$ different rats.
†Significantly different from control, $P < 0.0001$.
^{NS}Not significantly different from initial $BaCl_2$ response.

considerable importance. The small terminal (resistance) arterioles, located both on the brain's surface (pial vasculature used here) and in the deep tissues, are the major effector sites for regulation of adequate cerebral blood flow (Mchedlishvilli, 1980). The results of the present study clearly show that perivascularly applied lidocaine to the pial vasculature (0.1 ml of 0.1–20 mg/ml solutions), induces profound and dose-dependent increases in pial terminal arteriolar diameters. In each instance, only vessels with known resting tone were studied.

To our knowledge, no other drug or vasoactive substance has been shown to produce, like lidocaine, up to a 45% increase in pial terminal arteriolar size (Kuschinsky & Wahl, 1978; Altura *et al.*, 1980; Lassof & Altura, 1980; Mchedlishvilli, 1980). In rat mesenteric and cremaster muscle microvessels, the mean increase in terminal arteriolar diameter produced by topical application of lidocaine is 30–35% (Altura, 1971; 1978). Thus pial terminal arterioles, at least in the rat, are more sensitive to the local vasodilator action of lidocaine. Since a major portion of cerebral blood flow can be controlled by these pial vessels (Kuschinsky & Wahl, 1978; Mchedlishvilli, 1980; Siesjö *et al.*, 1980), the high degree of relaxation, induced by the local anaesthetic, may be of considerable importance. Since no hormone or endogenous vasoactive substance, that we have investigated, can produce vasoconstrictions or vasodilatations greater than 20–25% on the rat pial terminal arterioles, it is unlikely that lidocaine causes pial arteriolar dilatation through an indirect action by blocking or masking endogenous or released vasoconstrictor or vasodilator substances. It is thus tempting to speculate that the cerebral (pial) arteriolar dilator action of lidocaine that is described here, is brought about by a direct action on the cerebral arteriolar vascular smooth muscle cells. The latter would be consonant with current ideas about the actions of lidocaine on peripheral blood vessels (Altura & Altura, 1974).

Whether lidocaine can become a vital therapeutic tool in alleviating increased intracranial pressure (Bedford *et al.*, 1980), or cerebral vasospasm, will depend on finding a means by which adequate concentrations of this local anaesthetic can be infused into the cerebral circulation without invoking the disastrous sequelae of events noted in the peripheral circulatory system (Schumacher, Lieberson & Childress, 1968).

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