activity but much less than pyrogallol. The COMT inhibitor, catechol (1,2-dihydroxybenzene), did not appear to be active in this regard.

The finding that the blood pressure response to vasopressin is markedly affected by pyrogallol may have wide import because of the current interest in agents that affect the metabolism of catecholamines. It is now known that one of the major routes of degradation of epinephrine and norepinephrine is *via* o-methylation[5]. The enzyme involved, catechol o-methyl transferase, can be effectively inhibited by furnishing a competitive substrate, such as pyrogallol[6,7]. The presence of pyrogallol slows the destruction of epinephrine and norepinephrine and extends their duration of action[8,9]. However, vasopressin has long been classed as a direct-acting vasoconstrictor with a mechanism of action unrelated to catecholamines, and it was surprising, therefore, to find that a COMT inhibitor would modify its response. It is well known that adrenergic blocking agents do not prevent the pressor response to vasopressin, and NASH[3] has shown that complete depletion of catecholamines by reserpine pretreatment not only does not depress the response but actually increases it.

The data reported here might be interpreted as indicating an intimate relationship between catecholamines and vasopressin vascular effects. Support for this concept could be found in the work of GARDIER[10,11], who has demonstrated a relationship between the sympathetic nervous system and the effect of vasopressin on blood pressure. Other workers have implicated cyclic 3′,5′-AMP in the mechanism of action of both epinephrine and vasopressin[12,13].

In the present case, however, the weight of evidence opposes this view. In addition to the failure of adrenergic blockade or catecholamine depletion by reserpine to reduce the pressor action of vasopressin, it appears that certain other COMT inhibitors (e.g. catechol) do not have this action of pyrogallol. These data indicate that the COMT inhibiting action of pyrogallol is not the mechanism involved. The suggestion of a non-COMT inhibiting action is also supported by the recent work of HALMAGYI et al.[14], who have shown a pulmonary antispasmodic action of pyrogallol which is unrelated to COMT inhibition. Alternatively, it is suggested that pyrogallol is able to alter in some way the receptors for vasopressin or to increase the dissociation of vasopressin from its receptor complex in such a way as to permit repeated responses to occur. The basis for this action is obscure and requires further study[15,16].

Résumé. Le pyrogallol empêche le développement d'une tachyphylaxie à la vasopressine. Il restitue la réaction pressorique après l'apparition d'une tachyphylaxie. Cet effet ne semble pas être lié à l'action inhibitrice de cette substance sur l'enzyme transférase o-méthyl.

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The Effect of Isoxsuprine on the Motility Pattern of the Isolated Human Myometrium[1]

In a previous report[2] it was demonstrated that the action of prostaglandin on the isolated human non-pregnant myometrium could be affected by variations in the extracellular concentration of potassium. The normal effect of prostaglandin on the myometrium is that of inhibition. A decrease in the extra-cellular potassium concentration enhances the inhibitory response of human isolated myometrium to prostaglandin. However, the addition of prostaglandin to a myometrium placed in a potassium-rich bath fluid produces only a small inhibition of motility, or, in some instances, even induces a stimulation of the preparation.

In order to study the specificity of this effect of potassium on the reactivity pattern of human myometrium to prostaglandin, a similar study has been performed with isoxsuprine, a compound which also inhibits the spontaneous activity of the human myometrium[3].

The experimental conditions were the same as in the previous study, i.e. the motility of excised strips from the human uterus was studied *in vitro* using almost isometrical recordings. Four strips from each uterus were studied simultaneously, each strip mounted in separate 40 ml cuvettes in an organ bath. The bath fluid was a slightly modified Tyrode solution aerated with 5% CO_2 in O_2, pH being 7.35 ± 0.05. The active compound was always added to the bath diluted in 1 ml of a fluid with the same composition and temperature as the bath fluid. A continuous inflow of fresh Tyrode from below at a rate of 1.5 ml/min slowly washed away the added compound. This procedure was adopted since it gave stable experimental conditions and reproduceable results. For details the reader is referred to a previous communication[4].

In the present study 12 strips from three uteri all in late proliferative phase were used. The effect of isoxsuprine on the spontaneous motility of the isolated human myometrium under different extra-cellular potassium concentrations, 1–17 mEqv/l, was tested. The preparation used

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contained isoxsuprine (2-(phenoxy-2-propylamino)-1-(*p*, hydroxyphenyl)-1-propanol HCl) 5 mg, glycerine 25 mg, sterile water ad 1 ml (Duvadilan®) and was kindly put at our disposal by Ferrosan, Sweden.

In all experiments isoxsuprine caused an inhibition in the spontaneous motility of the human myometrium. The amplitude and the frequency of the contractions decreased while there was little or no effect on the tonus. The effect of isoxsuprine developed gradually with the maximal response occurring approximately 30 min after addition (Figure).

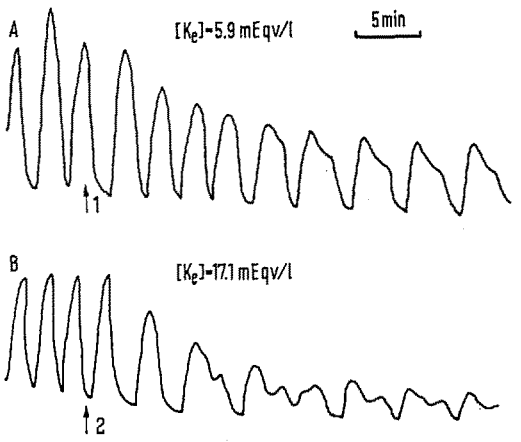
After the addition of isoxsuprine a gradual change in the motility pattern occurred which was characterized by a prolongation of the first phase in the relaxation period of each cycle (Figure).

In our experiments the threshold dose of isoxsuprine was approximately 10 µg/ml bath fluid. The addition of 25 µg/ml usually produced a 50% reduction in the amplitude of the contractions.

Variations of the extra-cellular concentration of potassium within the range of 1–17 mEqv/l did not elicit any change in the reactivity pattern of the myometrium to isoxsuprine. The inhibitory effect was not decreased by increasing the $[K_e]$ from 5.9 to 17.1 mEqv/l as illustrated in the Figure.

There are only a few compounds known to cause inhibition of the spontaneous motility of the isolated non-pregnant human myometrium, e.g. prostaglandin[4,5], bradykinin[6], and isoxsuprine[3]. In the present experiments it was shown that the isoxsuprine-induced response developed slowly, reaching its maximum effect approximately 30 min after the addition of the compounds to the bath. This was in agreement with the observations of Lish et al.[3], who found that the maximum effect was reached after about 1 to 2 h. The shorter time in our investigation may be attributed to the difference in the experimental procedure. The dramatic effect of isoxsuprine on the tonus of the myometrium demonstrated by Lish et al.[3] was not found in the present investigation. This difference may be attributed to the fact that an almost isometric recording of the motility was employed in the present study.

The human myometrium is rather insensitive to isoxsuprine, the threshold dose being in the order of 10 µg/ml, and a 50% inhibition being caused by 25 µg/ml. As a comparison it may be noted that a 50% inhibition is usually obtained with 0.05 µg of the crystalline compound



The effect of 25 µg isoxsuprine per ml bath fluid (1 and 2) on the motility of the isolated non-pregnant human myometrium in normal and high extra-cellular potassium concentration.

PGE_1[7] and with less than 0.2 µg bradykinin[6]. On the other hand, the rat uterus *in vitro* is highly sensitive to isoxsuprine, a dose of 0.01 µg/ml is usually sufficient to produce a 50% inhibition of motility[3]. However, the rat uterus is rather insensitive to prostaglandin and isolated preparations are always stimulated by this factor[5].

In contrast to the results obtained with prostaglandin and bradykinin, isoxsuprine caused a prolongation of the first phase of the relaxation (Figure). This type of reaction was seen in all experiments. It appears as if isoxsuprine not only decreases the amplitude of the contractions but also causes a partial 'blocking' of the relaxation process. A similar reactivity pattern has not been observed in the *in vivo* recordings from pregnant uteri[8,9] but this may be due to the recording system employed (i.e. measuring of the intra-amniotic pressure) and/or to a different reactivity pattern of the pregnant myometrium.

The present investigation was undertaken in order to ascertain if variations in the extra-cellular concentration of potassium would change the reactivity of the myometrium to isoxsuprine in a manner similar to the influence of potassium on prostaglandin, i.e. an increase in $[K_e]$ would decrease the response to a given dose and in some cases also change the reactivity pattern to that of stimulation. Variations in $[K_e]$ did not change the reactivity to isoxsuprine. The mode of action of prostaglandin and isoxsuprine is therefore not the same. An increase in the extra-cellular potassium concentration is known to decrease the sensitivity of the myometrium to, for example, electrical stimulation and to the stimulatory effect of acetylcholine. There was no sign of a decreased sensitivity to isoxsuprine when the potassium concentration was increased from 5.6 to 17.1 mEqv/l.

The mode of action of various stimuli on the myometrium is not known, but from our present experience it appears that the effect of isoxsuprine is rather unspecific and possibly due to blocking of some metabolic processes in the contraction-relaxation cycle.

In many respects the non-pregnant human myometrium reacts in a different way to pharmacological substances compared with other smooth muscle organs. Compounds that can inhibit the spontaneous motility of the uterus are of importance in the management of certain obstetric disorders and possibly also in some gynaecological problems, e.g. dysmenorrhea. Further studies on the reactivity pattern of the human myometrium to various autopharmacological and pharmacological compounds are therefore warranted.

Zusammenfassung. Isoxsuprine in einer Dosis zwischen 10 und 25 µg/ml Badflüssigkeit verursacht eine Hemmung der spontanen Beweglichkeit des isolierten nichtgraviden menschlichen Myometriums. Die Hemmung ist charakterisiert durch abgeschwächte Zusammenziehungen und durch verzögerte Entspannung. Ein Wechsel in der extrazellulären Kaliumkonzentration beeinflusst die Empfindlichkeit oder das Reaktionsmuster des Myometriums gegen Isoxsuprine nicht.

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