Mechanisms for the Secretion of ANP

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INTRODUCTION

The heart is an endocrine gland secreting a family of atrial natriuretic peptides (ANPs) involved in the regulation of body fluid and blood pressure. ANP is synthesized and stored in atrial cardiomyocytes, and secreted into the bloodstream by stimulations. ANP is stored in specific atrial granules of atrial cardiomyocytes as prohormone molecule which is unusually different from the pattern of storage of processed products. The classical physiological functions of ANP are mainly on the heart, kidneys and central nervous system (1~3, Fig. 1). Non-classical new functions are shown : examples are inhibitions of cellular proliferation (4) and secretions (5), and effects on sperm motility (6) and behavior (7). The synthesis of ANP is not confined to the atrium as previously reported. In the case of ventricular hypertrophy, congestive heart failure or myocardial infarction, ventricular ANP gene is reexpressed and ANP is synthesized (8, 9). The secretion of ventricular ANP is constitutively regulated (10). Extracardiac sites of ANP synthesis are among the many discrete tissues and organs including the brain, kidney, intestines, reproductive and immune systems (11~13). Many specific functions of ANP come from its different receptors; membrane-bound guanylyl cyclase coupled or noncoupled NPR (natriuretic peptide receptor)-A, NPR-B or NPR-C (14~16). The effects of activation of NPR-A and NPR-B are through the generation of cyclic GMP. The purpose of the present review is to describe some of the regulatory mechanism for the secretion of ANP, especially for the mechanically stimulated ANP secretion from the atria.

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HISTORICAL BACKGROUND

It has been suggested that the cardiac atrium is an organ integrating body fluid regulation (17). Henry et al. (17). showed that left atrial distension induced by a tiny balloon increased urinary flow. Several years later one of the mechanisms by which atrial distension increases urinary flow was defined by showing the involvement of antidiuretic hormone (18, ADH, arginine vasopressin, AVP). Many related studies repeatedly confirmed this phenomenon by showing that different maneuvers such as head-out water immersion and head-down position which increase central blood volume elevate urinary flow by way of the suppression of the plasma AVP levels.

On the other hand DeWardner et al. (19) suggested that saline infusion-induced diuresis/natriuresis is caused by a circulating "natriuretic factor". Many groups are searching for the "natriuretic factor". In 1981, DeBold et al. (20) wrote an article on the natriuretic factor from the cardiac atrium. Before this discovery several suggestions of cardiac involvement in body fluid regulation had been presented (Fig. 2). In 1956, Kisch (21) first reported on the presence of specific atrial granules in guinea-pig atria. Jamieson and Palade (22) suggested that the specific atrial granule is secretory in nature. Marie et al. (23), and three years later DeBold (24), showed that the secretory specific atrial granules change in size and number in response to the change in the body fluid and electrolyte balance. DeBold et al. (20) showed profound diuresis/natriuresis by an infusion of a crude atrial extract in rats. Later, it was confirmed that the specific atrial granules contain the natriuretic factor (25). After the discovery by DeBold et al. (20) of the atrial natriuretic factor, the sequence and cDNA of the atrial natriuretic factor were defined in 3~4 years (26~28). Active circulating forms of atrial natriuretic factor have C-terminal 24~28 aminoacids of prohormone composed

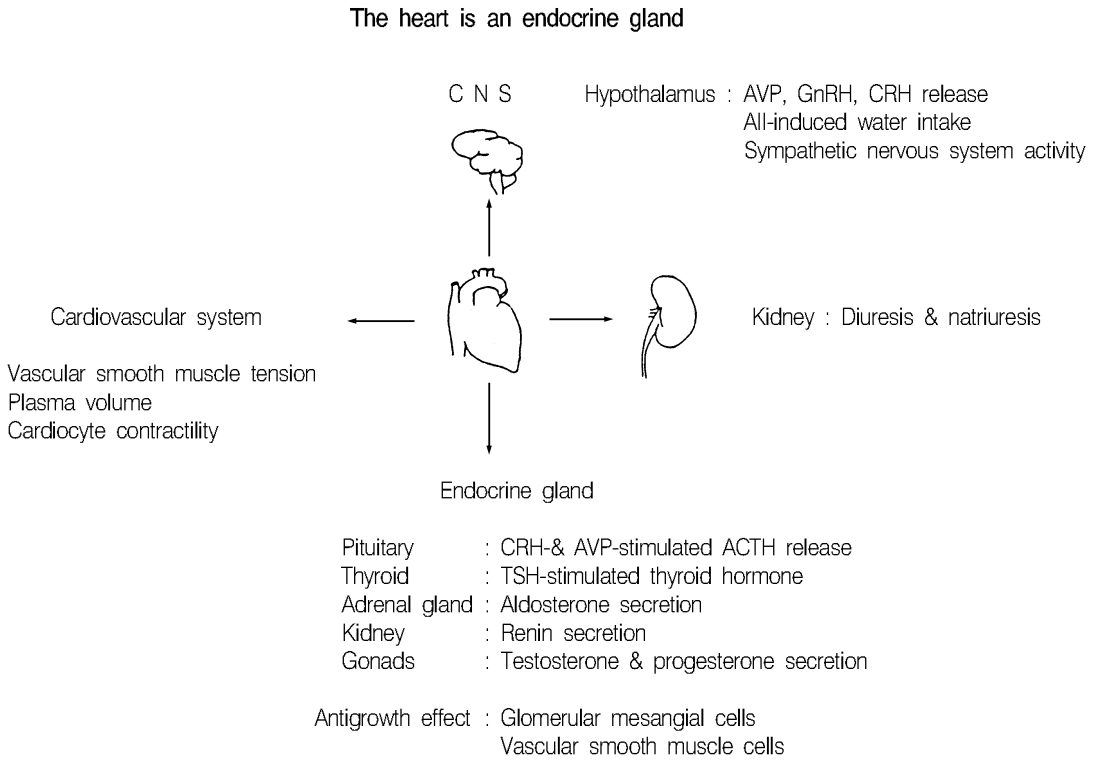

Fig. 1. Physiological functions of atrial natriuretic peptide.

of 126 aminoacids (proANP). ANP was synthesized in 1984 and a year later radioimmunoassay for ANP in plasma and tissues was established (29).

Dietz (30) and Lang et al. (31) showed that atrial distension or increase in atrial pressure is a factor which increases atrial secretion of ANP. Therefore, it is possible to explain the Henry-Gauer reflex, that increasing atrial distension increases urinary flow, in two ways shown in Fig. 3.

ANP, Historical background

1956	Henry-Gauer reflex
1956	Kisch
1964	Jamieson & Palade
1976	Marie et al
1979	De Bold
1981	De Bold et al
1983~4	Purified, sequenced & synthesized ANP
	cDNA cloned
1984~5	ANP RIA
	ANP in tissue & plasma
	ANP receptors
	ANP secretion mechanism

Fig. 2. Historical background.

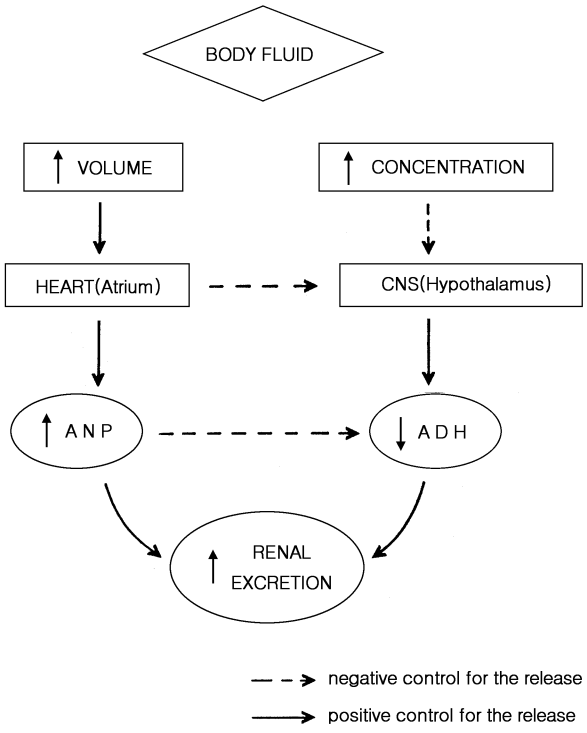

Fig. 3. An integration of atrial stimulation to increase urinary flow.

MECHANISMS FOR THE SECRETION OF ANP

Even though not a single but multiple factors are known to control the secretion of ANP, mechanical stimulation is considered to be the most prominent factor responsible for the regulation of the cardiac hormone secretion. The regulatory mechanism for the secretion of ANP through the chemical receptors on the sarcolemma is controversial (9). Adrenergic (32~35), cholinergic (33, 36, 37) and peptidergic (32, 38, 39) control mechanisms have been proposed. One of the most powerful stimulations for the secretion of ANP is produced by endothelin-1 (39) via endothelin receptor ET (A). The effect of endothelin-1 on ANP secretion is accompanied by a positive inotropic response.

Importance of atrial stretch in the regulation of ANP secretion: Dietz (30) and Lang et al. (31) showed that atrial distension or increase in atrial pressure is closely related to the increase in ANP secretion. Many different maneuvers which increase atrial pressure or distension were accompanied by an increase in plasma levels of ANP. Arginine vasopressin and angiotensin II caused an increase in plasma levels of ANP (40, 41). Even though the mechanism by which these agents increase plasma levels of ANP was not clearly defined, the change in atrial dynamics may be related to the ANP response. Volume expansion, head-down position and head-out water immersion which result in an atrial distension are also important factors related to the increase in plasma levels of ANP. Not only the atrial stretch but also the increase in atrial rate has been shown to be important in increasing plasma levels of ANP. It has been shown that paroxysmal atrial tachycardia increases plasma levels of ANP (42~45). As early as in 1963, Wood (46) was the first to show that the paroxysmal atrial tachycardia is related to the increase in urinary flow. The atrial stretch and increases in atrial pressure and rate are closely related to the increase in plasma levels of ANP.

Ruskoaho et al. (47) have shown very clearly that the secretion of ANP is positively related to the increase in atrial pressure in Langendorff rat heart preparation. Bilder et al. (48) and Schiebinger and Linden (49) have shown that the changes in atrial stretch and atrial rate are important in the regulation of ANP secretion in in vitro atrial strip preparation. It has been shown for the first time in this laboratory that the secretion of ANP is quantitatively correlated with the atrial volume change, i.e., atrial secretion of ANP is a function of atrial stroke volume (50~52, Fig. 4). These experiments have been done in the newly developed perfused atrial preparation by which very effective atrial stretch and release is possible. It is therefore concluded that the regulation of the atrial secretion of ANP is closely related to the mechanical function of the atrium.

MECHANICAL BASIS OF THE SECRETION OF ANP

Atrial volume changes: Atrial work load is the single most important regulator for the secretion of ANP in in vivo (45) and in vitro (52, 53) experiments. The regulator

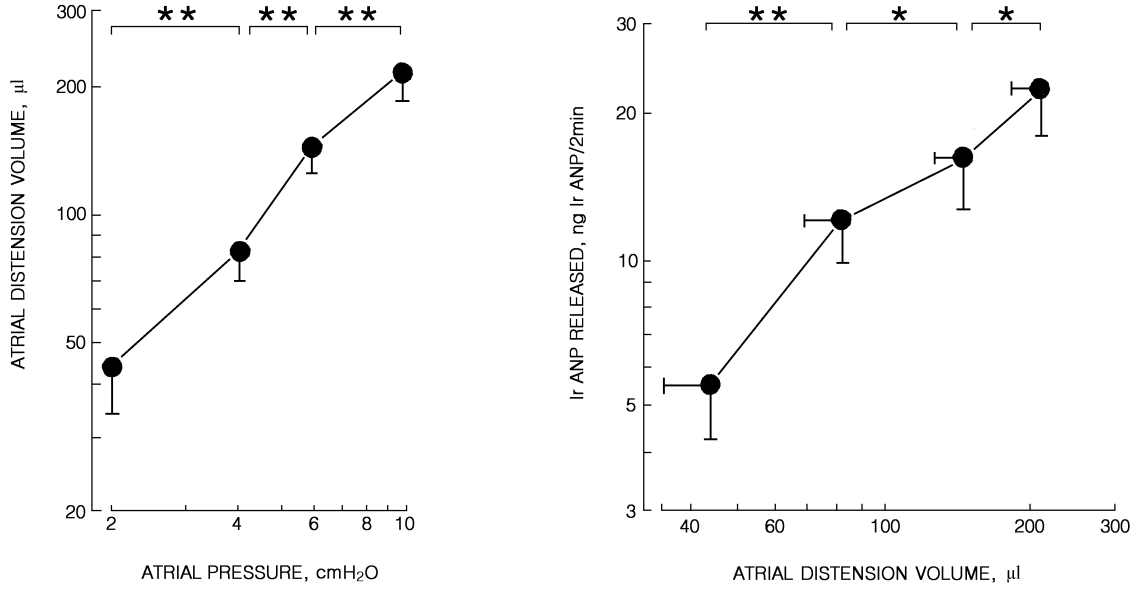

Fig. 4. Mechanically activated ANP secretion. Atrial volume change is caused by an increase in intra-atrial pressure (left). Atrial secretion of ANP is positively related with the change in atrial distension-and-reduction volume (right) (Ref. 50).

for the ANP secretion includes parallel factors, atrial stretch and release, and atrial pressure. Therefore, it is not easy to specify the responsible factor for the cause and response clearly. We have shown that the change in atrial pressure per se is not important for the regulation of ANP secretion (53, Fig. 5). Rather, the volume change induced by atrial reduction from the distension is important for predicting the ANP response to the mechanical stimulation (51). The volume changes induced by both active atrial contraction or passive release from the atrial stretch are well correlated with the

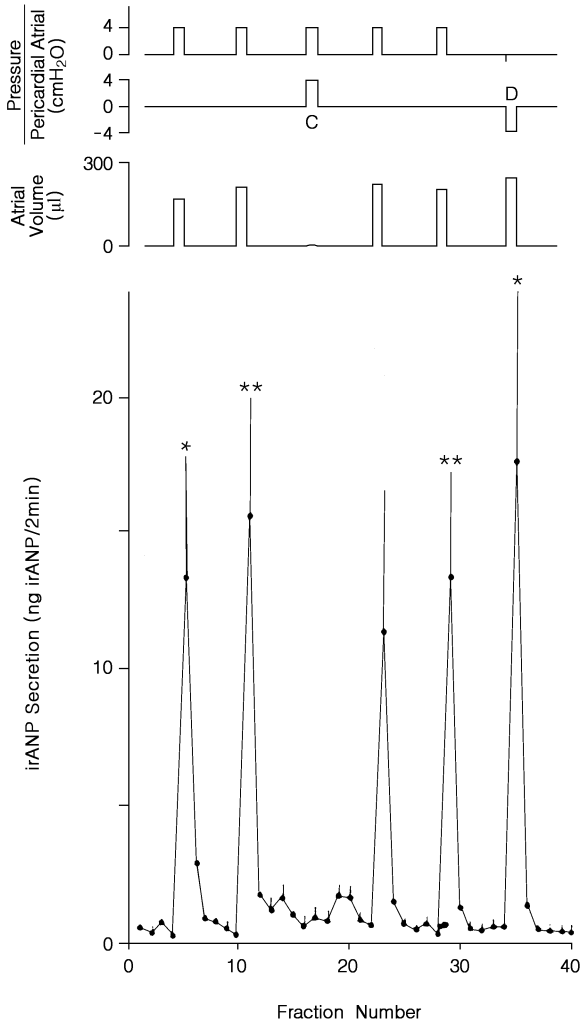

Fig. 5. Effects of intra-atrial and pericardial pressure changes on atrial distension-and-reduction volume and ANP secretion. Two control volume changes are followed by an intra-atrial pressure elevation with a simultaneous closure of the pericardial opening to prevent atrial distension at C. Neither atrial volume changes nor ANP response were observed. Alternatively, pericardial pressure depression at D results in an increase in transmural pressure and atrial distension with a transient small decrease in intra-atrial pressure. *P<0.05 **<0.025 vs. previous 2 periods (Ref. 53).

increase in ANP secretion (52, Fig. 6). It has been shown that the atrial endocardium has numerous folds and pouches which increase endocardial surface area (54). Considering the atrial structure with the extracellular fluid (ECF) translocation (vide infra), the step of atrial contraction is important in increasing the secretion of ANP through the atrial endocardium.

In this regard, the secretion of ANP has the predominant atrium (55), partly because both left and right atria have different structures in the endocardium (54) and ANP in the concentration (55, 56). The predominance of the atrium in ANP secretion has species variations.

Convective ANP secretion - a two-step sequential mechanism for the secretion of ANP: The mechanism by which mechanical stimulation increases ANP secretion is unknown. It has been found that there is an extracellular pathway through which atrial transmural transports of molecules are possible (57, 58). The pathway is bidirectional and its molecular cut-off range is around 57kda (58). Providing the pericardial 3H-inulin equillibrates the atrial intercellular space with extracellular marker. With this new technique it is possible to quantify the translocation of the ECF via the endocardium. The increase in ANP secretion by atrial contraction is accompanied by a simultaneous increase in the translocation of the ECF (52, 58, Fig. 6 & 7). The increase in ANP secretion induced by atrial volume changes is a function of the translocation of the ECF. Therefore, it could be concluded that an increase in atrial work results in an increase in the translocation of the ECF concomitantly with the ANP released. This means that the regulatory mechanism for the secretion of ANP includes a step of convection of ANP molecules. It is not clearly defined how endocrine humoral molecules appear in the bloodstream after their release from the endocrine cells. From this point of view this new finding is interesting. Atrial cardiomyocytes release ANP into the extracellular space and the released ANP is translocated with the ECF into the bloodstream by an atrial contraction. The appearance of ANP in the bloodstream is mainly via the atrial endocardium. Therefore, it has been proposed that ANP secretion is regulated by a two-step sequential mechanism. In a first step, ANP is released into the extracellular space resulting in an increase in extracellular ANP concentration. The second step is translocation of extracellular ANP into the atrial lumen by an atrial contraction. This second stage is an example of biological economics.

Mechanism for the release of ANP: The regulatory mechanism for the first step of ANP secretion, i.e., atrial

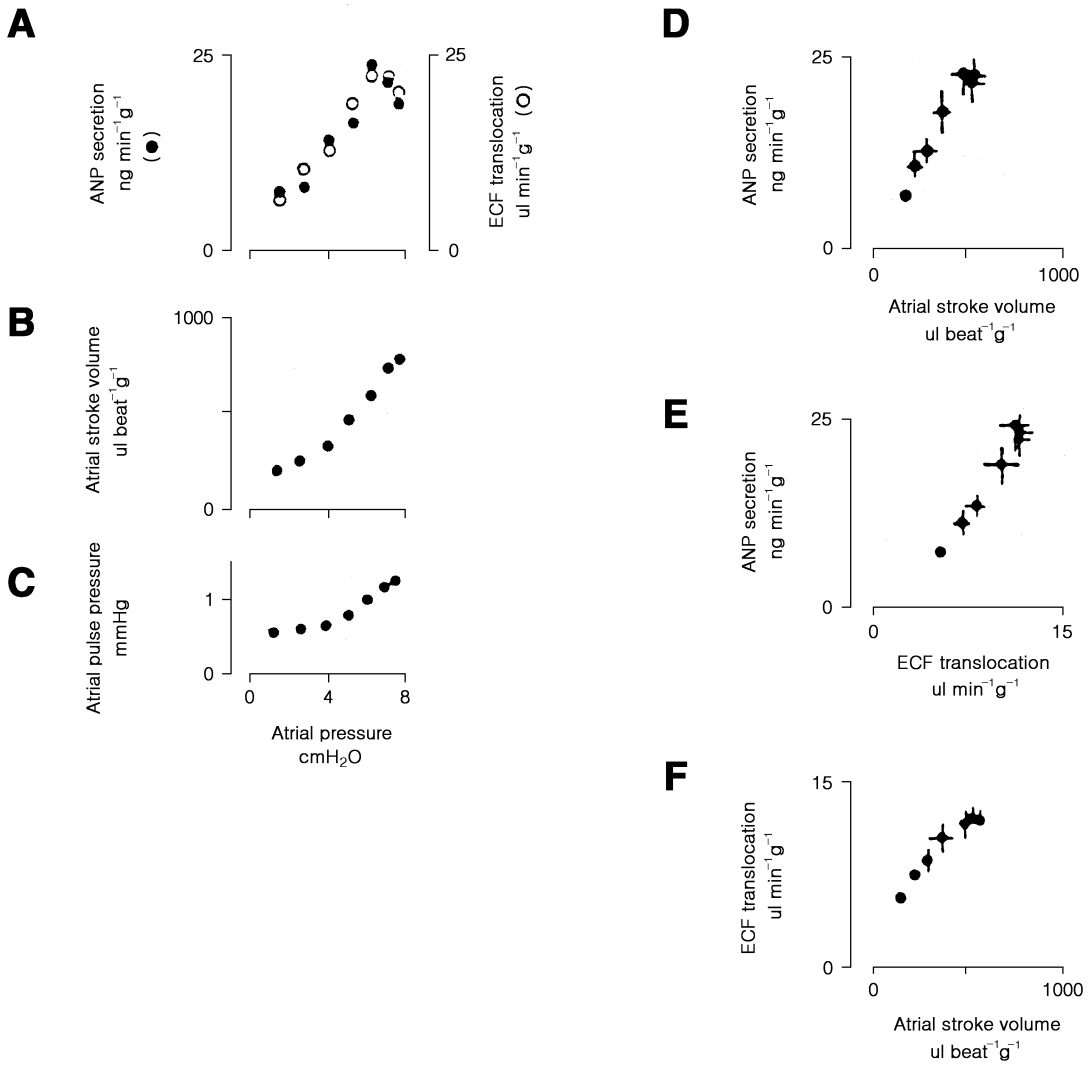

Fig. 6. Effects of an increase in atrial distension on ANP secretion, ECF translocation and atrial dynamic changes in paced atria (1.5 Hz). A-C, Representative experiments showing increases in ANP secretion and ECF translocation (A), atrial stroke volume (B), and atrial pulse pressure (C) in response to gradual increases in atrial distension. Increase in ANP secretion was plotted as a function of changes in atrial stroke volume (D) and translocation of ECF (E). F, increase in ECF translocation plotted as a function of simultaneous change in atrial stroke volume (Ref. 52).

release of ANP into the extracellular space has yet to be defined. The involvement of protein kinase C has been suggested in the regulation of ANP secretion (33). However, more precise experiments are needed. Roles for the Ca^{2+} in the regulation of ANP secretion have been proposed. There are two opposite opinions. Many researchers have shown that Ca^{2+} increases ANP secretion (59~61). On the other hand, others have claimed that Ca^{2+} is a negative regulator for the secretion of ANP (62~64). Even though different experimental approaches may be responsible for the discrepancy, the exact reason for the problem is not clear. Considering a two-step sequential mechanism for the secretion of ANP, both opinions have weak points in their experimental models. Atrial strips and cultured cells may not be a good simulation for the functioning cardiac atrium. The technique can not quantify the convective translocation of the ANP released. It has been shown that Ca^{2+} suppresses atrial release of ANP without changing the ECF translocation in non-beating atria (63, Fig. 8). It has also been shown that Ca^{2+} channel antagonist accentuates and Ca^{2+} channel agonist suppresses the atrial release of ANP in beating atria (65). These results suggest that Ca^{2+} is a negative regulator for the secretion of ANP. Recently, Xu et al. (66) reported on the involvement of K^{+}_{ATP} channels in the regulation of

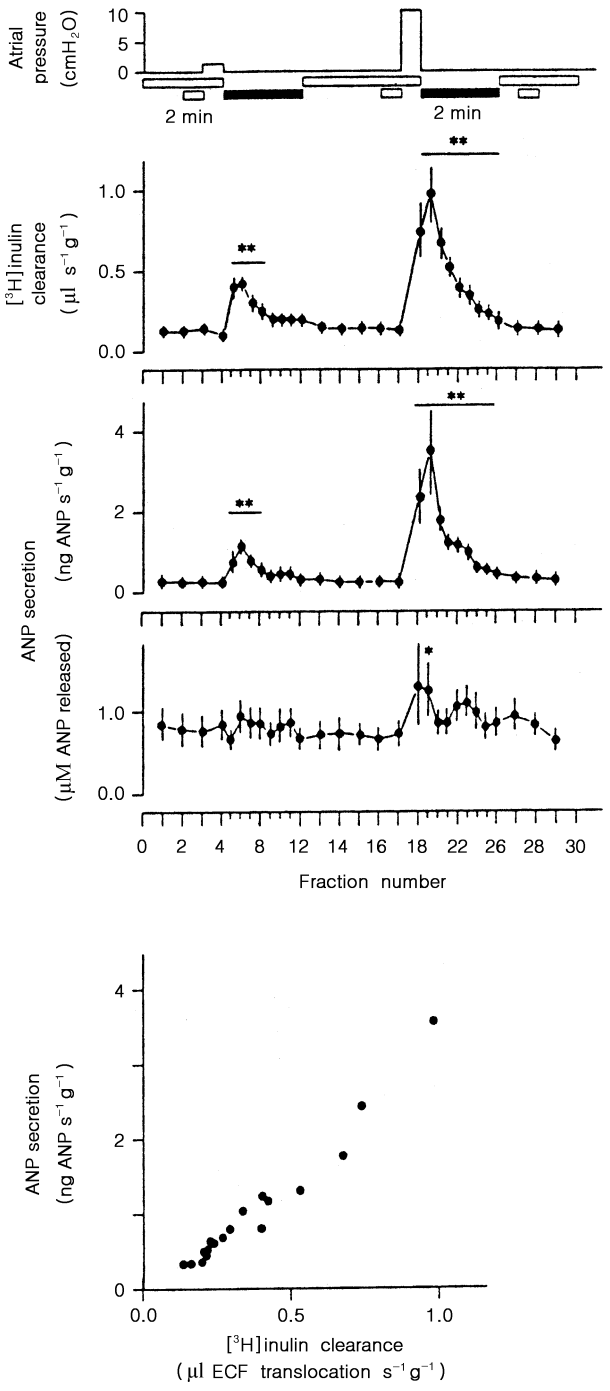

Fig. 7. Coincident increase in the ANP secretion with translocation of the ECF (upper). A reduction in atrial distension results in an increase in the ANP secretion coincident with an increase in the translocation of the ECF (3Hinulin clearance). Horizontal bars below the atrial pressure trace are markings for time period. The short open and filled bars represent 2 min. The atrial perfusate was collected 15 s fractions for 2 min following the reduction in atrial distension. Markings denote significantly different values. (Lower) Relation between ANP secretion and ECF translocation is shown (Ref. 58).

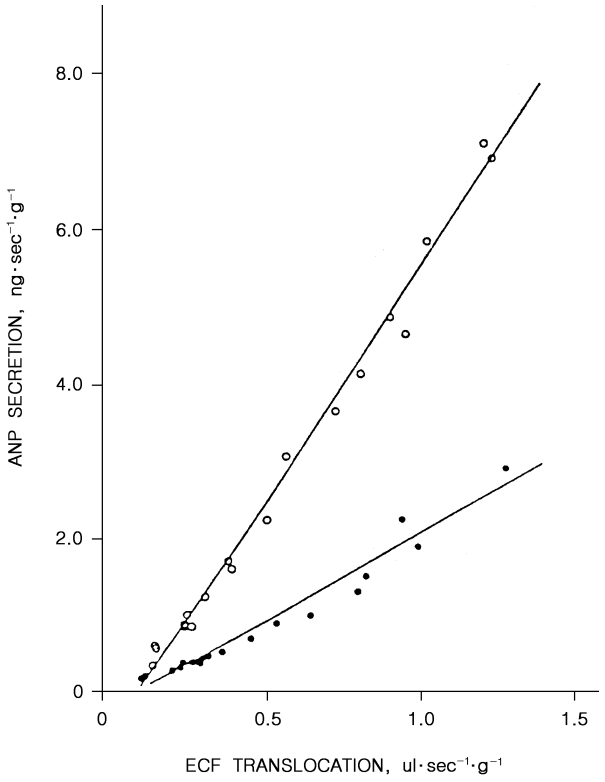

Fig. 8. Relation between changes in the translocation of the ECF and ANP secretion. Increase in the ANP secretion is significantly correlated with the translocation of the ECF (ANP secretion=2.31 ECF translocation - 0.26, r=0.983, P<0.001 for regular buffer, closed dots ; ANP secretion=6.12 ECF translocation - 0.66, r=0.995, P<0.001 for low Ca^{2+} buffer, open dots). The relationship for the atria perfused with low Ca^{2+} buffer was significantly different from that for the control atria perfused with regular buffer solution (Ref. 63).

ANP secretion. They claimed that blockade of K^+_{ATP} channels increased ANP secretion. However, Kim et al. (64) has clearly shown that blockade of K^+_{ATP} channels by glibenclamide suppresses the atrial release of ANP in non-beating atria. K^+_{ATP} channel opener reversed the suppression of ANP release by glibenclamide. Furthermore, they showed that the suppression of the atrial release of ANP by blockade of K^+_{ATP} channels is closely associated with extracellular Ca^{2+}. Therefore, this latter finding is consistent with the hypothesis that Ca^{2+} is a negative regulator for the atrial release of ANP.

Mechanomolecular signal transduction for ANP secretion: Even though the mechanical contraction of the atrium is a necessary final step for the appearance of ANP in the bloodstream, the first step of ANP secretion, i.e., atrial release of ANP, is still far from clear. Mechanosensitive ion channels have been found in atrial

cardiomyocytes (67). Mechanically activated Ca^{2+} channels may not be a positive regulator for the stretch-activated ANP secretion, because an increase in Ca^{2+} flux suppresses the atrial release of ANP. Actually, the accentuation of ANP secretion induced by increasing atrial rate contains a component of suppression of atrial release of ANP possibly related to an increase in intracellular Ca^{2+}(personal communication). Stretch-activated K^{+}_{ATP} channels (68) may be an important candidate for the positive regulation in the mechanically activated ANP secretion. It is possible that the stretch-activated ANP secretion is mediated by a yet unidentified mechanism. Mechanosensitive channels may be involved in the modulation for this signal transduction.

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