EDITORIAL COMMENT

Histamine, Mast Cells, and Heart Failure

Is There a Connection?*

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We have known about histamine receptors in the heart for many years (1). The human H$_1$- and H$_2$-histamine receptors were cloned and characterized in the early 1990s (2,3), followed closely by the human H$_3$- and H$_4$-histamine receptors several years later (4,5). Histamine is a natural body constituent that is found throughout the body, especially the central nervous system, mast cells, gastric mucosa parietal cells, and basophils. The H$_1$-receptor is coupled to G$_{s}$-q11 and activates a number of intracellular signals, including cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate. In the heart, histamine decreases atrioventricular node conduction time via H$_1$-receptors. The H$_2$-histamine receptors are also found in the heart, and couple to G$_{s}$ proteins to signal through cAMP to produce chronotropic and inotropic activity. The H$_2$-histamine receptors also subserve hypotension, flushing, headache, increased gastric acid production, and enhanced vascular permeability. Therefore, in essence, histamine is a true neurohormone.

Mast cells are found in the heart, where they are known to release histamine (6). Mast cells and histamine release have been implicated in heart disease (7,8), including the development of heart failure (9). Mast cells, in addition to histamine, seem to be a unique source of renin (10), and thus in some cases might contribute to local activation of the renin-angiotensin-aldosterone system (RAAS) in the heart, and all of the potential adverse consequences of that particular neurohormonal system. Using an isolated Langendorff preparation, Mackins et al. (11) have shown that cardiac mast cell-derived renin promotes local angiotensin formation, norepinephrine release, and arrhythmias in an ischemic/reperfusion model. Mast cell stabilization with cromolyn or iodoxamide attenuates this process (11).

It is bad enough that mast cells release renin and drive the local RAAS, although we have therapy to vitiate the downstream responses. The release of histamine from mast cells is another matter. Histamine is present in high concentrations in the human heart (12,13). Mast cells have been shown to be increased in myocardial hypertrophy (14), a known important component of myocardial remodeling and heart failure (15). The H$_3$-histamine receptors are especially a potential problem, because they are linked to classic Gs proteins and the production of cAMP, similar to norepinephrine and beta-adrenergic receptors. In animal studies, famotidine and cimetidine (H$_2$-histamine receptor blockers) attenuate ischemia-induced increases in myocardial cAMP accumulation (16). In principle, H$_2$-histamine receptor activation in the heart has the potential to drive cAMP much in the same fashion as excessive norepinephrine. If so, pharmacologic blockade of H$_2$-histamine receptor blockers ought to benefit the heart failure syndrome beyond blockade of the sympathetic nervous system and the RAAS. It must be remembered that despite our many successes in the treatment of heart failure, our current drug regimens probably prolong survival only about 9 to 18 months relative to where we were in 1985. We still need better therapies, especially those without significant hemodynamic adverse effects.

In this issue of the Journal, Kim et al. (17) reported their findings after taking advantage of an interesting technique—data mining for discovering useful information hidden in a database, a ploy used by chemical, financial, and insurance companies and similar to the concept of microarray analysis for genetic discoveries (18). This specific technique is rarely used in the medical field, in part because it necessitates accurate, complete, and consistent data entry. The analysis found that famotidine and proton pump inhibitors extend beneficial effects in patients with heart failure (18). From this point, they constructed the hypothesis that H$_2$-histamine receptor blockade may benefit patients with heart failure, and validated it retrospectively in a case-controlled study comparing H$_2$-histamine receptor blockade versus teprenone (an antiulcer drug independent of H$_2$-histamine receptor blockade). The investigators further tested the hypothesis prospectively in a small group of patients already treated with RAAS and beta-adrenergic blocking drugs (18).

For investigators using the cumbersome tool of large clinical trials to find beneficial new drugs, the road has been difficult. The annualized mortality for heart failure has dropped from 18% to 20% to about 6% to 8% on average. In principle, adding a drug such as famotidine allows for blocking a “hidden” neurohormonal target (H$_2$-histamine receptor) that may be playing a role in the pathophysiology of some patients with heart failure. At the end of the day, further reduction in cAMP may provide additional benefit for patients with heart failure, especially those intolerant to beta-adrenergic blockers or taking insufficient doses of beta-adrenergic blockers.

Articles such as this by Kim et al. (17) serve a useful but uncommon purpose. They introduce new ideas, fresh thinking, and alternative considerations. The concept of data

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mining is familiar to clinical investigators and outcomes researchers to uncover adverse drug effects, but the novel technique that this group used to uncover a pharmacologic target has not been used widely in the medical field. Any discoveries and hypotheses generated from data mining techniques should mandate: 1) the assurance of the reliability and completeness of the data that are being analyzed; 2) the scientific background understanding and the plausibility of the observations; 3) the availability of a comparably sensible competing hypothesis (i.e., null hypothesis) that may fare worse; and 4) the possibility of such a hypothesis to be tested prospectively in mechanistic studies, in particular to show the proposed mechanism(s). Clearly, the preliminary but provocative findings from years of work by Kim et al. (17) fulfill this discovery track. These data are unlikely reproducible in some existing administrative or pharmaceutical claims databases, particularly when data completeness and reliability may be questionable.

The H2-histamine receptor blockers are widely used, and are available over the counter. The rationale for using H2-histamine receptor blockers to treat patients with heart failure is relatively straightforward. However, we do not know what the quantitative contribution of mast cells is to the syndrome of heart failure. We need to find out more about the interactions between histamine, mast cells, and the heart failure syndrome. The safety and efficacy of this drug class in the broad heart failure population are yet to be established. The results reported by Kim et al. (17) have to be validated, and no one is recommending famotidine or any other histamine receptor blockers to treat patients with heart failure based simply on the existing information. Clearly, this interesting concept is very early in its development, and additional data regarding its efficacy and safety are required. However, we need some new and imaginative thinking in this arena, and perhaps this article will serve to provide that.

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