Lower Central Nervous System Serotonergic Function and Risk of Cardiovascular Disease
Where Are We, What’s Next?

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The second question whose answer will enhance our ability to apply knowledge of the role of CNS 5HT function in CVD pathogenesis to guide development of more effective approaches to prevention, treatment and rehabilitation is this: via what mechanisms do variations in CNS 5HT function influence CVD pathogenesis? As Muldoon et al have shown in their prior work, and convincingly confirm in the current report, reduced CNS 5HT function is associated with increased expression of most components of the metabolic syndrome. They also document that this increased expression of the metabolic syndrome mediates significantly, but not completely, the association they observe between reduced CNS 5HT function and greater maximum intima-medial thickness, indicating that effects of reduced CNS 5HT function on other predisease endophenotypes are also involved in pathogenesis.

One endophenotype that is a good candidate to account for additional variance in the effects of reduced CNS 5HT function on CVD pathogenesis is sympathetic nervous system--mediated blood pressure reactivity to psychological stress. Increased brain serotonergic neurotransmission achieved by loading with 5-hydroxytryptophan has been shown to decrease sympathetic nerve traffic in the cardiovascular system, and stimulation of 5HT1a receptors in medullary raphe nuclei produces concomitant decreases in sympathetic nerve discharge and mean arterial pressure. These findings combine with the demonstration that increased blood pressure reactivity to psychological stress is an independent predictor of increased coronary artery calcification to suggest that dysregulated CNS 5HT function may contribute to CVD pathogenesis via effects on sympathetically mediated cardiovascular reactivity to psychological stress. Other endophenotypes influenced by CNS 5HT function that deserve attention include decreased parasympathetic outflow, increased smoking, increased eating behavior and increased alcohol consumption.

These answers to the questions posed above suggest that to understand the role of CNS 5HT function in the pathogenesis of CVD and then use this knowledge to improve approaches to CVD prevention, treatment and rehabilitation, it will be necessary to mount a prospective longitudinal study in which a large and diverse sample of young and middle-aged adults is genotyped for all the genes that are known to regulate 5HT synthesis, release and reuptake and metabolism as well as those that encode for 5HT receptors that mediate effects of synaptic 5HT on CVD endophenotypes. In their prior work this same group has demonstrated the importance of variation in some of these genes by showing that functional polymorphisms in the 5HT transporter (5HTTLPR) and monoamine oxidase-A (MAOA-U VNTR) genes moderate the prolactin response to agents that increase synaptic 5HT in the CNS. Such 5HTTLPR genotype also influences levels of another index of CNS 5HT function—levels of the major 5HT metabolite 5HIAA in cerebrospinal fluid—but in ways that vary as a function of both race and gender. Such moderating effects indicate that the task of characterizing the role of 5HT-related genes in regulating CNS 5HT function and its effects on endophenotypes involved in the pathogenesis of CVD will be complex.
how those demands are met, etc—that contribute to pathogene-
isis, both directly and via interaction with candidate genes. As
this sample ages and CVD events accumulate, it will be possible
to use sophisticated statistical approaches—eg, structural equa-
tion modeling—to document which 5HT-related genes are
acting, either directly or via interaction with environmental
stressors, to influence those endophenotypes that are the final
common pathway to CVD events. The causal model that would
be tested by such a study is shown in the Figure.

I recognize that funding for such an ambitious study may be
hard to secure and that even if funding is secured it will be
decades before the results enable us to identify with sufficient
accuracy those who are at high risk and use the knowledge
gained about the mechanisms responsible for that high risk to
develop and implement effective preventive treatment and
rehabilitative measures. It may be possible, however, to use
studies that are already in progress, in which much of the needed
data are already being collected, to accomplish the ambitious
goals of the ideal study described above. The Atherosclerosis
in Communities (ARIC) study includes 15 792 individuals
who were aged 45 to 64 years at recruitment in 1985 to 1989.9
The Coronary Artery Risk Development in Young Adults
(CARDIA) study included 5115 black and white men and
women aged 18 to 30 years in 1985 to 1986.10 The National
Longitudinal Study of Adolescent Health (Add Health Study)
recruited a nationally representative sample of >20 000
adolescents in grades 7 to 12 in the United States in 1994 to
1995.11 All 3 of these ongoing longitudinal studies have obtained
DNA on all participants; and data are being obtained
relevant to most of the CVD endophenotypes, shown in the
Figure.

As these 3 large cohorts—with mean ages ranging from 28 to
75 at the present time—continue to be followed and CVD
events mount in number, it should be possible to achieve many
of the aims described above for the ideal study and thereby
confirm the validity of the causal sequence proposed in the
Figure. Such confirmation could then lead to the design of
interventions that target multiple points in the causal chain. A
key criterion in the early evaluation of these interventions will be
that they have a positive impact on the intermediate CVD
endophenotypes. As Muldoon et al note, treatment with SSRIs
has been reported to reduce expression of many of the endo-
phenotypes that have been associated with reduced CNS 5HT
function, and there is even evidence that treatment with SSRIs
also may reduce the incidence of CVD events. There is also
evidence that behavioral interventions that teach stress coping
skills reduce not only psychosocial risk factors but also blood
pressure both at rest and in response to psychological stress.12

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R.W. is a founder and major stockholder of Williams LifeSkills, Inc and
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of stress-related CVD.

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