Biomedicine and Diseases: Review

Serotonin reuptake inhibitors and cardiovascular diseases: a platelet connection

E. Maurer-Spurej
University of British Columbia, Department of Pathology, 2211 Wesbrook Mall, Vancouver, British Columbia V6T 2B5 (Canada), Fax: +604 822 7135, e-mail: emaurer@interchange.ubc.ca

Received 16 June 2004; received after revision 9 September 2004; accepted 23 September 2004

Abstract. Selective serotonin reuptake inhibitors (SSRIs) are a heterogeneous group of new antidepressants that cause a well documented acquired but reversible serotonin deficiency in blood platelets. Platelets are small, anucleate cells and are the only blood cells specialized in storing peripheral serotonin. Platelets are also an integral part of the hemostatic process that is initiated during pathologic thrombus formation in cardiovascular diseases. Serotonin release from platelets is important for functional hemostasis as indicated by congenital diseases with serotonin-deficient platelets that can lead to life-threatening bleeding problems. The postulate that SSRIs should have an impact on cardiovascular diseases is therefore well founded. Cardiovascular effects of SSRIs have indeed been shown in a number of studies investigating the effect of SSRIs in patients with psychosomatic comorbidity. SSRIs reduce the incidence of recurrent myocardial infarction (MI) in patients suffering from post-MI depression. In addition, SSRIs inhibit tight clot formation of platelets in vitro, which points to a direct anti-thrombotic or pro-fibrinolytic effect of SSRIs.

Key words. Platelets; serotonin; selective serotonin reuptake inhibitors; cardiovascular disease.

Introduction

A platelet connection between selective serotonin reuptake inhibitors (SSRIs) and cardiovascular diseases (CVDs) would undoubtedly originate in the exclusive ability of platelets to take up and transport serotonin. Serotonin is a potent biogenic amine exhibiting strong vasoactive properties, possibly through stimulation of serotonin receptors on endothelial cells and through nitric oxide production [1, 2]. Serotonin is widespread in nature, found in fruit and vegetables such as pineapple and tomato [3], as well as in the neuronal systems of all organisms from Drosophila [4] to humans [5]. Tryptophan is the amino acid precursor of serotonin. Tryptophan hydroxylase (tph) and amino acid decarboxylase convert this essential amino acid into serotonin [6, 7], whereby tryptophan hydroxylation is the rate-limiting step. In birds and mammals, including humans, serotonin levels in the central nervous system represent only a small fraction of the total serotonin in the body. Serotonin is also independently produced in peripheral tissues [8]. In these organisms, enterochromaffin cells in the intestine produce serotonin and release it into the blood. Interestingly, two different tryptophan hydroxylase isoenzymes synthesize serotonin in serotonergic neurons of the raphe nuclei (tph2) and in peripheral tissues (tph1) [9]. Highly efficient uptake and transport systems for peripheral serotonin have evolved, namely platelet or thrombocyte dense granules [10]. Serotonin uptake into dense granules protects the organism from serotonin-induced uncontrolled, harmful vasoconstriction or vasodilation [11]. Although many aspects of platelet serotonin transport are well characterized, such as the serotonin (5-HT) transporter (5-HTT or SERT) [12], the serotonin receptor 5-
HT₂A [13] and dense granule formation and release [14–16], the full function and role of platelet serotonin transport is still unknown.

Platelets have been viewed and used as neuronal models of serotonin uptake and release for the past 50 years. Beginning in the 1970s, platelets and neurons were found to be similar with respect to serotonin uptake, and platelets were used as easily accessible neuronal models [17–20]. However, the interest in platelets as neuronal models diminished quickly because of the sensitivity of platelets to environmental stress [21–23], as well as the difficulty of measuring peripheral serotonin reproducibly [24, 25]. The discovery that SSRIs are effective antidepressants has revived such interest, since SSRIs block the reuptake of serotonin into neurons [26] as well as platelets [27–29]. To exploit this analogy, it has been suggested that pretreatment levels of platelet serotonin in samples from depressed patients might predict therapeutic outcome for at least some SSRIs [27]. Thus, the platelet model could be a useful clinical tool for monitoring the effect of antidepressants. It is by now well documented that prolonged intake of certain SSRIs, especially at high concentrations, leads to a significant decrease in platelet serotonin [28–31].

CVDs are conditions that affect the proper functioning of the heart and blood vessels, chief among which are myocardial infarction (MI, heart attack), cerebrovascular disease (stroke), transient ischemic attack (TIA) and peripheral vascular diseases. CVDs, principally heart disease and stroke, are the leading cause of death for both men and women among all racial and ethnic groups in developed countries [32]. Although CVDs can be treated or prevented, an estimated 17 million people die of CVDs each year, and at least 10% of the victims are between 35 and 64 years old.

Platelets clot in response to vessel wall injury at the acute stage of CVD, release their granule content [33] and exert both positive and negative feedback for platelet recruitment to the clot [34, 35]. Serotonin release during occlusive coronary thrombus formation has been found to increase clot stability and ischemia due to vasoconstriction [36, 37].

This review summarizes the published effects of SSRIs on platelets. Particular emphasis was placed on the inhibition of serotonin release and concomitant diminished interaction with endothelial cells, smooth muscle cells, platelets and plasma proteins, because these are all potential contributors to the cardiovascular effect of SSRIs. The controversial literature related to benefits and risks of SSRIs in patients with cardiovascular diseases led to warnings about the use of SSRIs in these patients. However, most studies investigated the effect of SSRIs on depressed patients with CVD, which significantly complicates the interpretation of these results.

**Platelet serotonin**

Looking for an agent in the blood responsible for hypertension, Maurice Rapport, Arda Green and Irvine Page discovered serotonin in 1948 [38] and named it for its presence in serum (sero-) and its vasoactive properties (-tonin). Serotonin was identified as 5-hydroxytryptamine (5-HT) and shown to be identical to enteramine that had been extracted from stomach and intestine [39]. The past 3 decades have seen an enormous increase in interest in and knowledge about the neurotransmitter serotonin. However, while interest in brain serotonin exploded, spurred by discoveries of its important roles in mood disorders, research on circulating serotonin has not kept pace. Initially, platelets were viewed as easily obtainable models for neurons because platelets share the serotonin receptor subtype 5-HT₂A and the expression of the serotonin transporter with neurons.

In humans, almost all circulating serotonin is transported by platelets in dense granules. It is long known that serotonin is a weak platelet agonist, but its effect is enhanced by ADP and epinephrine [40]. Two important issues related to serotonin as platelet agonist should be noted. First, under normal conditions the plasma levels of serotonin are very low, 0.1–10 ng/ml compared to a mean of 884 ± 202 ng/10⁹ platelets measured by high-pressure liquid chromatography (HPLC) with electrochemical detection [31, 41, 42]. With a special gas chromatography-mass spectrometry method normal plasma serotonin levels were reported to be even lower, with a range of 0.05–0.3 ng/ml [43]. However, it was found that platelet-activating concentrations have to exceed 1 μM [44]. This means that the high serotonin concentrations required for platelet activation are only available after release from dense granules in response to other agonists. It has also been shown that strong activation is required in order for dense granule release to occur [45]. Second, loading of radiolabeled serotonin requires incubation of platelets with 2 μM concentrations of serotonin generally for 30 min at 37°C. This procedure is not known to activate human platelets as it does not affect platelet morphology or platelet surface markers.

Figure 1 shows a schematic summary of the four most important interactions of peripheral serotonin after release from platelet stores: (1) interaction with endothelial cells, (2) direct and indirect interaction with smooth muscle cells, (3) platelet activation via positive feedback within the platelet clot and (4) binding to alpha-granule proteins. Among the possible responses of platelets to stimulation by serotonin are serotonylation of small GTPases of the RhoA family [46] and phosphorylation of extracellular signal-regulated protein kinase 1/2 (ERK 1/2) [47]. Although the involvement of small GTPases in dense granule release has long been discussed, their serotonylation has not been unequivocally demonstrated.