Platelet α -adrenoceptors—A valid model for brain or vascular adrenoceptors?

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α -adrenoceptors are widely distributed and, directly or indirectly, subserve a range of behavioural, circulatory and metabolic roles. Receptors are located pre- and postsynaptically in brain and at pre- and post-junctional sites in the periphery. At least two receptor subtypes, α_1 and α_2 , have been identified and important differences between the two subtypes in the influence of divalent and monovalent cations in binding to the receptor, and in the role of calcium and coupling to adenylate cyclase have been described. Many important therapeutic approaches are based on modification of α -adrenoceptor function. For α_2 -adrenoceptors for example agonists and antagonists are the basis of pharmacological approaches to treatment of hypertension and depression respectively.

Although there are well established methods of studying *in vivo* vascular α_1 -adrenoceptors (Sumner *et al.*, 1982) and vascular α_2 -adrenoceptors (Elliott & Reid, 1983) in intact man, and of studying vascular responses in the forearm bed (Kiowski *et al.*, 1983; Jie *et al.*, 1984), it is not easy to apply newer techniques of radioligand binding to peripheral vascular tissues and even more difficult to obtain human brain tissue. There is thus interest in developing model systems which can be applied to brain or vascular receptors. Blood elements, red cells, white cells, and platelets are accessible and can be safely sampled on repeated occasions. Changes in β -adrenoceptors on the surface of lymphocytes have been used as an index of β -adrenoceptors in other tissues (Colucci *et al.*, 1981; Piantonelli *et al.*, 1984). α -adrenoceptors have been identified on platelets. Radioligand binding studies firstly using [3 H]-dihydroergocryptine (Alexander *et al.*, 1978) and later [3 H]-yohimbine (Daiguji *et al.*, 1981) have confirmed that there are high affinity binding sites on platelets which have the characteristics of α_2 -adrenoceptors. Moreover the aggregatory response of platelets to adrenaline can be stimulated by selective α_2 -adrenoceptor agonists and inhibited by α_2 -adrenoceptor antagonists like yohimbine and idazoxan confirming the α_2 -adrenoceptor classification

of the platelet adrenoceptor and providing a simple measure of functional response for the platelet α -adrenoceptor (Grant & Scrutton, 1979). Thus, in view of accessibility and ease of sampling, the platelet has been widely adopted as a model of α_2 -adrenoceptor systems not only of peripheral vascular α -adrenoceptors but also of receptors in the central nervous system.

Changes in platelet aggregation and α_2 -adrenoceptor number in depressive disorders have been correlated with changes in central α_2 -adrenoceptor density (Garcia Sevilla *et al.*, 1981, 1983) as has the effectiveness of therapy with tricyclic antidepressant drugs (Garcia Sevilla *et al.*, 1981). Correlations between platelet α_2 -adrenoceptor number and the severity of the abstinence syndrome in heroin addicts have also been reported (Garcia Sevilla *et al.*, 1984). This has led to the suggestion that platelet α_2 -adrenoceptors may be used as a model to study receptor mechanisms of opiate withdrawal. Platelet α_2 -adrenoceptors are altered by circulating levels of sex hormones (Elkeles *et al.*, 1968; Caspary & Peberdy, 1965). Changes in platelet α_2 -adrenoceptor number may occur during the menstrual cycle (Jones *et al.*, 1983) and in premenopausal women taking the oral contraceptive pill (Peters *et al.*, 1979). The number of platelet α_2 -adrenoceptors also falls in postmenopausal women (Elliot & Grahame Smith, 1982) and postpartum (Metz *et al.*, 1983). It has been suggested that such a decrease in α_2 -adrenoceptor number might be related to mood disorders such as 'maternity blues' occurring at these times. Finally, platelet α_2 -adrenoceptor number and function has also been investigated in relationship to blood pressure sympathetic activity and antihypertensive therapy in attempts to explore further the pathophysiology of hypertension (Kafka *et al.*, 1979; Motulsky *et al.*, 1983; Jones *et al.*, 1985). No clear picture has emerged from these studies; no change in receptor number or affinity, increases and decreases in number, all having been reported. Treatment with the antihypertensive α_2 -adrenoceptor agonists clonidine and guanabenz have also produced conflicting results, both

a decrease (Brodde, 1983) and no change in platelet α_2 -adrenoceptor number (Motulsky *et al.*, 1983) being found. Overall these studies suggest that there is no direct correlation between platelet α_2 -adrenoceptor number and blood pressure and that lowering blood pressure *per se* does not influence receptor number.

Although extrapolations from platelet to other α_2 -adrenoceptors are not uncommon, until recently there have been few studies in which changes in platelet adrenoceptors were directly compared to those in other tissues. In a number of these studies, tissue and species specific changes in α_2 -adrenoceptor number and response have been observed under physiological conditions. In the female rabbits maturation results in a decrease in platelet α_2 -adrenoceptor number and attenuation of α_2 -adrenoceptor mediated aggregation in platelets but no changes in kidney or brain α_2 -adrenoceptors (Mishra *et al.*, 1985a), while in older male animals a decrease in number in brain but not spleen or platelets has been observed (Hamilton *et al.*, 1986). In man, with increasing age, decreases in the responsiveness of vascular postsynaptic α_2 -adrenoceptors (Docherty & Hyland, 1985a), no change in presynaptic α_2 -adrenoceptor mediated responses (Docherty & Hyland, 1985a) but an increase in the aggregatory response of platelets to adrenaline (Johnson *et al.*, 1975) have been reported. In contrast in the rat decreases in α_2 -adrenoceptor mediated responses in the vasculature and at presynaptic α_2 -adrenoceptors in the vas deferens may occur with ageing (Docherty & Hyland, 1985b; Docherty & O'Malley, 1983) although increases in postsynaptic α_2 -adrenoceptor mediated responses in the vas deferens have been observed (Lai *et al.*, 1983).

Drug and hormone modulation of α_2 -adrenoceptor number may also be tissue specific. In the rabbit, oestrogen treatment increases the number of α_2 -adrenoceptors in the uterus and bladder (Elliot *et al.*, 1980; Roberts *et al.*, 1977) but decreases that in the platelet and causes no change or a relatively small decrease in number in brain, spleen and kidney (Mishra *et al.*, 1985b; Roberts *et al.*, 1979), while amitriptyline treatment has been reported to attenuate responses to intracisternal clonidine and reduce the number of α_2 -adrenoceptors in the high affinity state in rabbit hindbrain without causing concomitant changes in platelet α_2 -adrenoceptor number or aggregation (Hamilton *et al.*, 1986). Differences between tissues in susceptibility to down regulation by the endogenous agonists noradrenaline and adrenaline may also occur, high circulating levels of catecholamines being reported to cause down regulation of α_2 -adrenoceptors on plate-

lets and neuroblastoma cells but not in kidney or liver (Davies *et al.*, 1981; Kahn & U'Prichard, 1981; Snavely *et al.*, 1983). Agonist efficacy, differential accessibility of the receptor to drugs and hormones, and differences in the rate of metabolism of the receptor by the cells on which they are situated could all affect the rate of desensitisation and down regulation and contribute to apparent tissue selectivity. As well as receptor degradation, the rate of receptor synthesis may also vary between tissues. It may be slower in brain than in many peripheral tissues (Hamilton & Reid, 1985) as protein synthesis may occur in cell bodies with axonal transport to terminals or dendrites while in the platelet recovery will be related primarily to platelet turnover and release from the marrow. Differences in receptor synthesis will result in different rates of recovery from down regulation after the agonist is withdrawn. Thus the platelet which does not have the capacity to synthesise new receptor protein may not always be a suitable model for studying events such as first dose effects, tolerance and withdrawal which may be related to drug induced changes at vascular and central adrenoceptors.

Differences in the coupling of receptor activation to response or in receptor subtypes between tissues could also result in differences in receptor mediated responses to drugs, hormones, physiological and pathological events. There is some evidence that the α_2 -adrenoceptor on the platelet may not be a good model for α_2 -adrenoceptors in all other tissues. α_2 -adrenoceptors are generally believed to be negatively coupled to adenylate cyclase via a guanine nucleotide binding protein. However, there is controversy as to whether a reduction in intracellular cAMP levels is responsible for platelet aggregation and whether inhibition of cAMP is the only mechanism by which platelet α_2 -adrenoceptor activation leads to a response (Clare *et al.*, 1984; Swart *et al.*, 1985). There may also be tissue differences in α_2 -adrenoceptor subtype. Several groups have suggested that there is α_2 -adrenoceptor heterogeneity (Drew, 1985; Waterfall *et al.*, 1985; Dickinson *et al.*, 1986), the major difference being between α_2 -adrenoceptors from rodent and non-rodent species. Rodent α_2 -adrenoceptors have a much higher affinity for prazosin than those from other species and can be classed α_2B while non rodent α_2 -adrenoceptors which have a comparatively high affinity for oxymetazoline may be classed α_2A . More pertinent to this review Bylund (1985) has suggested that although rodent tissues contain predominantly α_2B adrenoceptors, within a species the proportion of α_2A and α_2B adrenoceptors may vary

between tissues. In rat neonatal lung 100% of the α_2 -adrenoceptors are of the B subtype in rat cerebral cortex 43%, while in corpus striatum only 6% are of the B subtype. In man the α_2 -adrenoceptors on the platelet are all A adrenoceptors, however, it should not be assumed that all α_2 -adrenoceptors are A. The relative affinity of prazosin to yohimbine for α_2 -adrenoceptor binding sites is lower in human adipocytes than platelets (Richelsen & Pedersen, 1985; Cheung *et al.*, 1982) which could suggest that adipocytes contain some α_2 -B adrenoceptors.

In summary, platelets have been used as a model of α_2 -adrenoceptors in a wide range of studies in man. In these studies changes in platelet α_2 -adrenoceptor number or function have been extrapolated to α_2 -adrenoceptors in other tissues. Conclusions have been drawn about the role of α_2 -adrenoceptors in pathogenesis and therapeutic responses in disease states. However, other studies show many drug and hormone

changes in α_2 -adrenoceptor number and function to be tissue specific. Extrapolation from platelets to other tissues may be unjustified and misleading in view of the many factors which modulate and regulate adrenoceptor function.

Considerable caution should be exercised in the interpretation and extrapolation of results from platelets to other α -adrenoceptors. Firstly the other receptors must be α_2 in type and other local factors modulating receptor number and function must be excluded. Under some circumstances the platelet α_2 -adrenoceptor may reflect other non-innervated peripheral receptors like the post junctional vascular α_2 -adrenoceptor as both appear to respond to circulating adrenaline and will be regulated by the level of peripheral sympathoadrenal activity. In contrast pre and postsynaptic receptors in brain and prejunctional receptors in the periphery appear to be under intrasynaptic regulatory influences and may not be comparable to platelets studied *in vitro*.

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(Received 20 June 1986,
accepted 18 July 1986)