BIOCOMPATIBILITY OF ACTIVATED CARBONS

S. V. Mikhalovsky, T. A. Alexeeva, E. A. Fesenko**, N. T. Kartel*, and V. V. Strelko**
University of Brighton, School of Pharmacy and Biomolecular Sciences, Cockcroft Building, Lewes Road, Brighton BN2 4GJ, U.K.
**Institute of Sorption and Problems of Endoecology, Kiev, Ukraine*
***University of Huddersfield, School of Applied Sciences, Queensgate, Huddersfield HD1 3DH, U.K.*

Introduction

Although extracorporeal adsorption techniques (haemo- and plasma perfusion) have been introduced along with dialysis and filtration, application of the adsorbents has been practically limited to acute poisoning caused by low molecular weight substances. Such a restriction is a consequence of poor haemocompatibility of adsorbents that have been initially used for haemoperfusion [1]. Direct contact between the blood and activated carbon resulted in a severe loss of calcium, potassium and blood cell damage. Microparticles released from the carbon surface migrated through the bloodstream blocking narrow blood vessels and causing microemboli. Coating of sorbent granules with a semipermeable biocompatible membrane such as cellulose has solved the problem but at the same time reduced efficiency of the treatment [2]. Apparently, the best performance of haemoperfusion would be achieved using uncoated activated carbons whose haemocompatibility is at least equal to that of the coated adsorbents. In this paper experimental methods improving biocompatibility of medical activated carbons are discussed.

Experimental

Activated carbon SCN was produced by pyrolysis and steam activation of spherical crosslinked styrene-vinyl-pyridine copolymer. Oxidised SCN was prepared by carbon treatment with dilute nitric acid. Activated carbon KAU was produced by pyrolysis and steam activation of crushed apricot stones. In cyclic adsorption experiments a solution was perfused over a carbon column with peristaltic pump. In the experiments on fibrinogen adsorption 0.4 ml of the human blood plasma was incubated with 30-40 mg of activated carbon (AC) for 30 min at 37ºC.

Results and discussion

The most important parameters of haemoperfusion are efficiency and rate of removal (adsorption) of the target substance from the bloodstream. Coating of AC even with a thin membrane dramatically reduces the rate of adsorption of low molecular mass solutes (Table 1). A membrane virtually cuts off HMW molecules and significantly reduces adsorption of "middle molecules" with molecular mass between 300 and 15,000 [3]. Removal of 'middle molecules' is essential as they play an important role in the development of many pathological conditions.

Table 1. Adsorption of methylene blue on coated and uncoated AC in cyclic experiments*.

AC	Column/ Company	Mass of AC/ Column volume	$\tau_{50\%}$, min	$\tau_{95\%}$, min
Cellophan-coated, 3-5 μm, Norit RBX, peat	Adsorba 300C/ Gambro	300 g/ 600 mL	39	154
Polyester-embedded, coconut shell	Hemo-detoxifier/ Becton, Dickinson	90 g/ 250 mL	115	>180
SCN		130 g/ 450 mL	5	14
KAU		150 g/ 450 mL	22	78

*Experimental conditions: initial concentration - 500 mg/L, solution volume 6 L, flow rate 125 mL/min, 25ºC

To make uncoated AC haemocompatible it is necessary to solve the problem of microparticle generation and to prevent release of any leachates into the bloodstream. Use of synthetic polymers as the precursor material allows strict control of the chemical purity of carbons, completely eliminating leaching of impurities in contact with the blood. The problem of microparticle generation is also solved by using polymer-pyrolysed active carbons that combine high mechanical strength with well developed porosity. Initially AC release microparticles into solution but after several washings with saline the number of microparticles in the range of 1-5 micron released from AC remains within the limits permitted by the British Pharmacopoeia for solutions injected into the blood (Fig. 1). It is interesting to notice that washing of AC column from 'bottom to top' is less efficient than from 'top to bottom', but the column with uncoated SCN is as clean as the coated Adsorba 300C column. Pre-treatment of medical carbons with solutions mimicking the mineral composition of blood practically solves the problem of the loss of ions or the change of pH (Fig. 2). Pre-treatment of AC with plasma protein solutions reduces fibrinogen adsorption (Table 2). Fibrinogen is the major factor responsible for blood clotting, and reducing its adsorption improves

haemocompatibility of biomaterials. Different effect of human serum albumin, HSA (67 kD), and immunoglobulin IgG (150 kD) on SCN and KAU is likely to be related to the difference in their mesopore size, the latter being substantially larger in KAU (over 50 nm compared to 36 nm in SCN).

Table 2. Fibrinogen adsorption from the human blood plasma on untreated and pre-treated activated carbons.

Carbon	Fibrinogen adsorption, %		
	Untreated	+ 0.2% HSA	+ 0.2% IgG
SCN	28	0	7.3
KAU	39	22	11

Due to the non-selective nature of adsorption, active carbons arguably remove nutrients and other essential blood components such as glucose and vitamins. This, however, is not a problem if haemoperfusion is used in acute cases, where this procedure is used once or repeated only a few times. There is not much data available for chronic patients, but it seems that use of a replacement fluid containing most important nutrients would prevent their depletion. In comparison with other extracorporeal techniques, haemoperfusion over uncoated AC should be considered as equally biocompatible. It is a more efficient treatment with regard to the removal of high and middle molecular solutes thus offering new opportunities for treatment of immune dependent diseases.

Conclusions

Haemocompatibility of activated carbon can be significantly improved by (i) washing out microparticles loosely bound to the granules and (ii) its pre-treatment with a solution adjusting the surface chemical composition to the mineral composition and pH of blood. Such a pre-treatment eliminates complications usually associated with use of uncoated carbon for direct blood perfusion.

References

1. Mikhalovsky SV. Ch. 5. Microparticles for hemo-perfusion and extracorporeal therapy. In: Microspheres, Microcapsules and Liposomes, The MML Series, Vol. 2: Medical & Biotechnology Applications, R. Arshady, Ed., Citus Books, London, 1999, pp. 133-169.
2. Chang TMS. Artificial Cells. C.C.Thomas Publ., Springfield, ILL, 1972.
3. Vanholder R, De Smet R, Vogeleere P and Ringoir S. Middle molecules: toxicity and removal by hemodialysis and related strategies, Artif Organs 1995;19:1120-1125.

Acknowledgements

This work was partly sponsored by INTAS grant N 94-3033 and Royal Society/NATO Fellowship (for EAF).

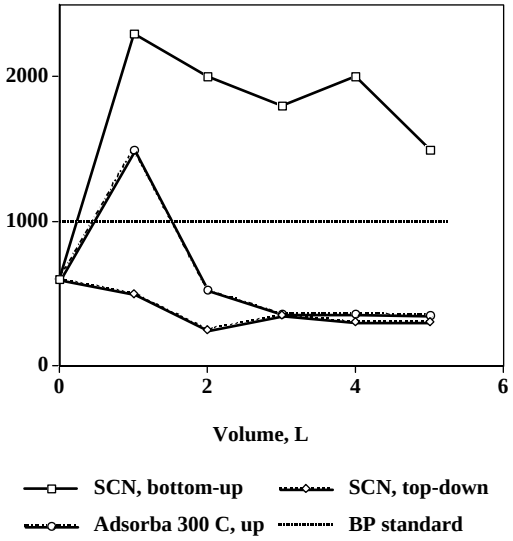

Fig. 1. Number of microparticles, per cm^3, released from AC after washing with saline.

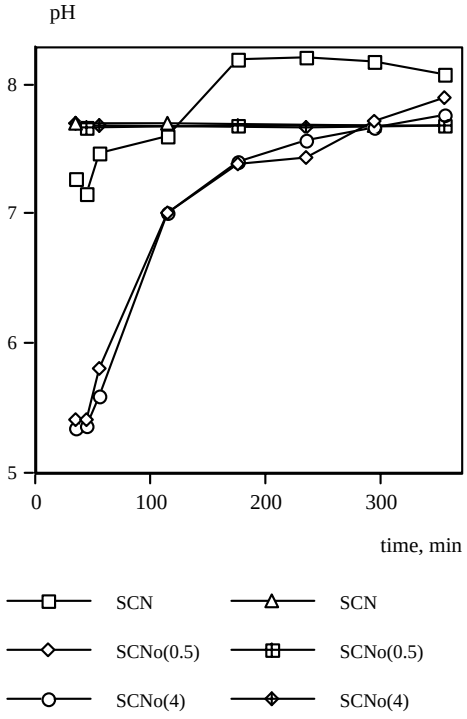

Fig. 2. Change of pH of the Tyrode's buffer (pH 7.69) in contact with AC.

Left column - no pre-treatment; right column - ion balanced AC. Numbers in brackets are the hours of oxidation with nitric acid.