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Short Communications

Long-term depressor effects of noradrenaline and dopamine neurons transplanted into the third ventricle of the brain of salt-loaded hypertensive rats

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Summary. Neural tissues including A6 group noradrenaline neurons in the locus ceruleus or A10 group dopamine neurons in the substantia nigra were transplanted into the third ventricle at the preoptic-anterior hypothalamic level of rats made hypertensive by salt loading. Either transplant exerted a long-lasting depressor effect.
Key words. Neural transplants; catecholamine neurons; third ventricle; salt hypertension; depressor effects.

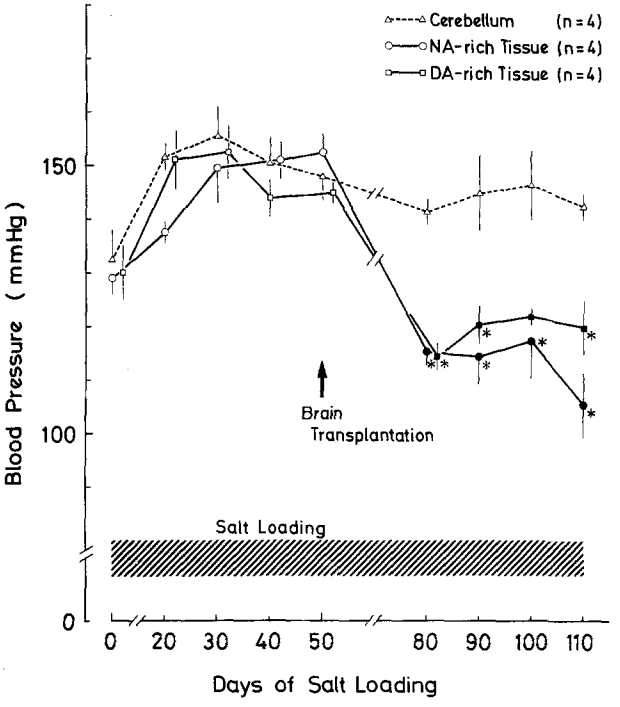
In the course of a previous study in which we assessed the effects on gonadotropin secretion of the transplantation of catecholamine (CA) neuron-rich brain tissue into the third ventricle (IIIV) at the level of the preoptic area (POA) [1], it was occasionally found that rats with such transplants had a blood pressure considerably lower than that in control rats without transplants (unpublished observation). There is ample evidence that brain catecholamine plays a role in decreasing arterial blood pressure [2–10]. It seems that the POA-anterior hypothalamic area (AHA) contributes to the depressor system [11, 12], the function of which is stimulated by CA transmission and is probably mediated by the nucleus tractus solitarius (NTS) [13]. Electrical stimulation of the AHA lowered blood pressure [14, 15]. In addition, the administration of CA, either noradrenaline (NA) or dopamine (DA), in the POA-AHA and NTS induced a decrease in blood pressure in

rats[16-17] and the activity of NA and DA in these areas is low in genetic[13,18-20] and renovascular[21] hypertension. It was therefore assumed that our rats transplanted with CA neuron-rich tissues in the IIIV showed a hypotension due to such an action of CA. The present study was undertaken to check this hypothesis by transplanting CA neurons into the IIIV of rats made hypertensive by salt loading.

Methods. Salt hypertension was induced in 8-week-old male rats of the Wistar strain with 2% NaCl given in place of their drinking water. The hypertension was fully developed in about 30 days, at which time blood pressure in all rats was significantly higher than before the salt loading was begun (fig.). Transplantation of CA neuron-rich tissues was performed in these hypertensive rats as described elsewhere[1]. Briefly, the tissue including A6 group NA neurons in the locus ceruleus or A10 group DA neurons in the substantia nigra was punched out of the coronal slice dissected from the medulla or midbrain of newborn rats with a metal cannula and was stereotaxically positioned in the IIIV at the POA-AHA region. Tissues from the cerebellum were transplanted as control transplants. Blood pressure and heart rate were measured in conscious rats by the indirect tail-cuff method using the rat-tail manometer system (KN-210, Natsume Seisakusho Co.).

At the termination of the experiment the rats were decapitated and the brains were rapidly taken out to be subjected to histological examination, as described elsewhere[1]. Only the data from the rats which were evaluated as having had surviving transplants in contact with the POA-AHA region were included in the results. It was confirmed in the previous study utilizing CA fluorescence method that such surviving transplants surely contained CA neurons[1].

Results. Blood pressure before and after the CA neuron transplantation is graphically shown in the figure as the mean ± SE for each NA, DA or control transplant. The rats with the transplants, either of NA- or DA-rich tissue, showed a marked decrease in blood pressure. Mean blood pressure 30 days after the transplantation surgery, i.e., at 80 days of salt loading, was significantly lower than at 50 days of salt loading. The values were even lower than those before the salt loading was begun, and were significantly lower ($p < 0.001$) than the value in control rats, which remained high. The hypotension continued to be stable for more than 60 days, during which time observation continued. The heart rate, which was increased significantly concurrently with an elevation of blood pressure following salt loading, dropped significantly with the transplantation surgery in all rats (table). It recovered to the level observed before the salt loading was begun, at 50 days after the surgery, in rats with control transplants, whereas the level remained significantly low in rats transplanted with CA neurons. At 60 days, the heart rate in rats with the transplantation, either of NA- or DA-rich tissue, was significantly lower than in rats with cerebellum transplantation.



Effects of transplantation into the third ventricle of brain tissues including catecholamine neurons on the blood pressure in the rat under salt loading. Tissues from the locus ceruleus or substantia nigra, as noradrenaline neuron-rich tissue (NA-rich tissue) and dopamine neuron-rich tissue (DA-rich tissue), respectively, were transplanted into rats which had become hypertensive due to salt loading. Cerebellar tissues were implanted as controls. Values are shown as the mean ± SE for each NA, DA or control transplant. * $p < 0.05$ vs controls.

Discussion. In the present study, transplantation of CA neurons into the IIIV in contact with the POA-AHA region was markedly effective in decreasing blood pressure in rats made hypertensive by salt loading. Further, the effect seemed to be stable, not permitting rebound rises, and long-lasting. Although it was not examined in the present study whether CA fibers of the transplant definitely formed synapses with the recipient neurons and further, if so, whether synapses so formed worked similarly to the intrinsic ones, the possibility has been presented that CA neurons re-established synapses resembling normal ones, when they were transplanted into the striatum that had undergone denervation of intrinsic CA

Effects of transplantation into the third ventricle of the brain tissues including catecholamine neurons on the heart rate in the rat under salt loading

Days of salt loading	0	20	30	40	50	80	90	100	110
Transplants	Heart rate (bpm)								
Cerebellum (n = 4)	405 ± 1	440 ± 11	440 ± 10	445 ± 18[a]	433 ± 17	369 ± 13[b]	350 ± 11[a, b]	386 ± 8[b]	387 ± 13[b]
NA-rich Tissue (n = 4)	403 ± 18	425 ± 16	419 ± 17	445 ± 17	438 ± 17	391 ± 14	342 ± 11[a, b]	362 ± 16[b]	342 ± 5[a, b, *]
DA-rich Tissue (n = 4)	393 ± 9	425 ± 16	428 ± 15	440 ± 17	432 ± 21	364 ± 13[b]	331 ± 17[a, b]	352 ± 11[b, *]	326 ± 14[a, b, *]
					(Brain transplantation)				

Values are shown in Mean ± SE. Numbers in parentheses show the number of rats in each group. [a] $p < 0.01$ or 0.05 vs values at 0 days. [b] $p < 0.01$ or 0.05 vs values at 50 days. * $p < 0.05$ vs values for rats with transplantation of cerebellum at corresponding days.

neurons[22], and in the lateral ventricle[23] and the lateral cortex that were destroyed[24]. Further, CA was actually released in almost normal quantities from the DA-denervated striatum which had been re-innervated by transplants of neonatal substantia nigra[25]. It is assumed therefore that the present effects have been produced by CA released from the transplanted neurons, although objective data on the brain content of CA would be necessary to draw a definite conclusion. The study measuring the CA content in the POA-AHA region or in the CSF of transplanted animals is now in progress.

The present results are in agreement with the previous observation that the administration of NA into the POA-AHA region decreases blood pressure[16], and suggest that the administration of DA in this region will also cause hypotension. It is therefore probable that the activity of the depressor system in the POA-AHA region is supported by both NA and DA transmissions. The results further demonstrate that the neural transplantation method is able to produce long-lasting hypotensive effects in rats loaded with salt.

In genetically and renovascularly hypertensive rats the activity of both NA and DA in the POA-AHA region was lower than that in normotensive rats, as mentioned earlier[13,18-21]. With the hypotensive effects of CA administered in these areas, it has been assumed that the impairment of CA metabolism in these areas is one of the factors responsible for the development and/or maintenance of hypertension. It was also suggested that the salt hypertension was accompanied by a reduction in the activity of AHA[26]. The present findings provide evidence indicating the importance of CA transmission in the activity of the POA-AHA region in salt hypertension.

Although we have focussed on the POA-AHA region as the site of action of CA released from the transplanted neurons, it is also possible that the NTS is affected by CA via the CSF. By acting at both sites, the CA released from the transplants can decrease blood pressure more effectively. This possibility will be clarified by measuring CA content in the CSF.

It has been postulated that, while the POA-AHA participates in the depressor system, inhibiting sympathetic nerve activity, it also works as a vagal center and produces bradycardia[27,28]. It was pointed out that electrical stimulation of the AHA could elicit a response pattern of combined sympathetic inhibition and vagal activation in the cardiovascular system[29]. In agreement, the administration of CA in the POA-AHA or NTS induced a decrease in the heart rate concomitantly with a decrease in blood pressure[16,17]. The present finding, i.e. the bradycardia existing comcomitantly with hypotension in rats with transplantation of CA neuron-rich tissues, appears to support the concept. The decrease in the heart rate observed shortly after the transplantation surgery in all rats would be a nonspecific response to the surgical stress, although the precise mechanism is unclear.

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