Neurotoxicity of strawberry Artificial flavour (Benzyl Acetate) on some neurotransmitter contents in male albino rats.

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Abstract: flavour strawberry (Benzyl Acetate) a widespread Artificial flavoured used in many food products, fast foods, beverages and soft drinks in Saudi Arabia. This research aims to study the effect of artificial flavour strawberry on some neurotransmitters content particularly norepinephrine (NE), dopamine (DA), serotonin (5-HT) and gamm-aminobutyric acid (GABA) in different brain regions. The results indicate that oral administration of Artificial flavour strawberry lead to a significant reduce in the content of neurotransmitter in the different brain areas, benzyl acetate may be induce neurotoxicity by conjugation with glycine it will changes in the neurotransmitter levels and lead to motor activity behavioral changes in the rat.
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1. Introduction

Artificial flavours the largest class of additives, function to make food taste better. flavouring agents, such as benzaldehyde for strawberry, cherryor almond flavour, may be used to simulate natural flavours. At this moment, food flavour enhance tasting food therefore it is popular [1-2]. In fact, a typical strawberry aroma (benzyl acetate) is consist of mixed more than 50 aromatic chemicals that does not come from strawberries. However, this flavouring is clearly recognized as strawberry by consumers [3].

benzyl acetate a colorless liquid is the most popular strawberry aroma. It used widely in soft drink, foods such as chewing gum, cake, desserts, yoghurts, vitamins. A number of previous studies show that this flavouring lead to pain in neck, headache and chest [4]. In addition, for children there is relationship between the consumption of benzyl acetate and hyperactive behavior [5]. It is also increased the incidences of pancreatic acinar cell and hepatocellular adenomas in rats[6].

Results of a recent research on the effects of benzyl acetate indicated that it highly affect on neurobehavioral, seizures, neuronal decomposition and astrocyte reactivity when high doses of benzyl acetate was intaken [7-8]. There is a lack of information about the influence of benzyl acetate on neurobehavioral. Therefore, the aim of this study was to investigate the effects of benzyl acetate on some neurotransmitters content in different brain areas in male albino rats.

2. Materials and Methods

2.1 Chemicals:

Benzyl acetate artificial flavour strawberry were Chiemical (Sigma Aldrich Chemicals, Mil- waukee, WI).

2.2 Animals:

The study was conducted in the Department of Zoology, King Abdul Aziz University in Saudi Arabia (Jeddah). Male albino rats, Rattus rattus (70 g - 100 g) was examined. They were housed in cages and supplied with food and water adlibitum under standard conditions of light, humidity and temperature (22°C - 25°C).

2.3 Experimental Design:

2.3 Animal Treatment:

Tow groups of rats were classified randomly. Control group (n=6) has treatment by saline vehicle then killing. Another group (n=24) has daily orally administered for 4 week with benzyl acetate(230 mg/ kg b.w) using oral tube, six rats were killed during experiments period 1, 2, 3 and 4 weeks.

2.4. Method

2.4.1. The effect of benzyl acetate on examined brain regions

The rats were chosen randomly from cage and killed. The approach Glowinski and Iversen was followed, the tissues of brain were quickly and carefully extirpated then positioned on dry ice glass plate [9-10]. The following region were separated: Cerebellum, striatum, cerebral cortex, hypothalamus, brain steam and hippocampus. The brain tissues were wiped dry to measure NE, DA and 5-HT according to the method of [11]. GABA was measured according to the method [12]. Jenway 6200 fluorometer was used to measure the fluorescence.

2.5. Statistical Analysis:

Mean ±S.E and percent were calculated to represent the data. Paired student test were performed [13].

3. Results

Results of the effect of daily oral administration of benzyl acetate(230 mg/ kg b.w) on norepinephrine were presented in tables. Table (1) shows a noticeable reduced in NE content in all brain regions starting from the 2nd week until the last period of experiment. The highest decrease in NE content ($p<0.05$) was noticed in the Striatum after 4 weeks (-80.95%).

Table (2) shows a noticeable reduced in DA content in all brain regions starting from the 2nd week until the last period of experiment. The highest decrease in DA content ($p<0.05$) was noticed in the hypothalamus after 4 weeks (-59.88%).

Table (3) shows a noticeable reduced in 5-HT content in all examined regions starting from the 4 week until the last period of experiment. The highest decrease ($p<0.05$) in 5-HT level was noticed after 4 weeks in the Cerebellum (-44.48%).

Table4 shows a noticeable reduced in GABA content starting in all brain regions from the 2nd week untill the last period of experiment. The highest decrease in GABA level was noticed after 4 weeks in the hippocampus (-69.72%).

Table (1): Effect of chronic oral administeration of the benzyl acetate (230 mg/ kg b.w) on norepinephrine (NE) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean ± S.E.	Striatum mean ± S.E.	Cerebral cortex mean ± S.E.	Hypothalamus mean ± S.E.	Brain stem mean ± S.E.	Hippocampus mean ± S.E.
1 week	C	95.382 ± 0.845	511.473 ± 1.803	56.203 ± 0.225	596.997 ± 3.242	390.050 ± 0.831	292.540 ± 1.536
	T	96.187 ± 0.474	513.399 ± 0.931	55.940 ± 0.928	605.997 ± 1.344	386.436 ± 2.100	292.176 ± 0.707
	%	0.84	0.38	-0.47	1.51 *	-0.93	-0.12
2 weeks	C	95.358 ± 0.857	511.118 ± 1.648	54.443 ± 1.898	605.330 ± 9.485	390.490 ± 0.484	292.527 ± 1.531
	T	55.167 ± 1.276	99.167 ± 0.980	42.500 ± 0.885	486.333 ± 1.647	104.000 ± 1.155	98.833 ± 0.477
	%	-42.15 *	-80.60 *	-21.94 *	-19.66 *	-73.37 *	-66.21 *
3 weeks	C	98.688 ± 0.274	495.653 ± 1.445	55.493 ± 0.105	604.906 ± 2.337	394.485 ± 0.942	283.178 ± 0.817
	T	48.667 ± 0.760	104.667 ± 0.558	42.167 ± 0.749	457.833 ± 1.138	152.833 ± 1.108	100.333 ± 1.745
	%	-50.69 *	-78.88 *	-24.01 *	-24.31 *	-61.26 *	-64.57 *
4 weeks	C	98.485 ± 0.271	509.167 ± 2.272	55.525 ± 0.127	604.623 ± 2.261	394.618 ± 0.944	282.998 ± 0.841
	T	43.833 ± 0.477	97.000 ± 0.577	40.627 ± 0.881	403.167 ± 1.078	102.833 ± 1.833	87.167 ± 0.792
	%	-55.49 *	-80.95 *	-26.83 *	-33.32 *	-73.94 *	-69.20 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t* ' test.
% : Percentage of change from control. * : Significant at $p<0.05$.

Table (2): Effect of chronic oral administeration of the benzyl acetate (230 mg/ kg b.w) on dopamine (DA) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean ± S.E.	Striatum mean ± S.E.	Cerebral cortex mean ± S.E.	Hypothalamus mean ± S.E.	Brain stem mean ± S.E.	Hippocampus mean ± S.E.
1 week	C	146.755 ± 0.818	473.948 ± 0.856	60.488 ± 0.044	734.223 ± 2.111	451.288 ± 0.633	243.147 ± 0.863
	T	145.163 ± 0.540	475.871 ± 1.208	60.658 ± 0.717	726.300 ± 3.542	454.680 ± 1.816	241.194 ± 0.763
	%	-1.09	0.41	0.28	-1.08	0.75	-0.80
2 weeks	C	144.935 ± 0.937	482.330 ± 3.344	60.993 ± 0.293	744.577 ± 2.855	451.706 ± 1.900	245.027 ± 1.381
	T	124.000 ± 0.966	402.167 ± 0.601	53.833 ± 0.307	553.833 ± 0.872	401.333 ± 0.494	199.000 ± 0.365
	%	-14.44 *	-16.62 *	-11.74 *	-25.62 *	-11.15 *	-18.78 *
3 weeks	C	146.977 ± 0.942	474.115 ± 0.911	60.715 ± 0.259	734.057 ± 2.258	451.606 ± 0.591	242.968 ± 0.843
	T	122.667 ± 0.760	223.833 ± 0.872	53.549 ± 0.563	353.500 ± 0.563	215.833 ± 0.601	156.333 ± 0.615
	%	-16.54 *	-52.79 *	-11.80 *	-51.84 *	-52.21 *	-35.66 *
4 weeks	C	146.100 ± 1.156	482.780 ± 3.194	62.328 ± 0.946	738.215 ± 4.439	451.637 ± 1.987	244.905 ± 1.544
	T	116.334 ± 1.604	196.000 ± 0.516	49.973 ± 0.330	296.333 ± 0.494	217.167 ± 0.872	156.167 ± 1.014
	%	-20.37 *	-59.40 *	-19.82 *	-59.86 *	-51.92 *	-36.23 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t* ' test.
% : Percentage of change from control. * : Significant at $p<0.05$.

Table (3): Effect of chronic oral administration of the benzyl acetate (230 mg/ kg b.w) on serotonin (5-HT) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean ± S.E.	Striatum mean ± S.E.	Cerebral cortex mean ± S.E.	Hypothalamus mean ± S.E.	Brain stem mean ± S.E.	Hippocampus mean ± S.E.
1 week	C	192.457 ± 0.799	171.652 ± 0.450	57.247 ± 0.385	432.828 ± 0.319	118.155 ± 0.197	214.787 ± 1.321
	T	186.520 ± 0.559	168.333 ± 1.776	55.508 ± 0.688	431.429 ± 0.915	115.185 ± 1.056	213.724 ± 0.291
	%	-3.09 *	-1.93	-3.04	-0.32	-2.51 *	-0.49
2 weeks	C	193.045 ± 0.719	171.496 ± 0.522	57.374 ± 0.463	433.106 ± 0.485	118.368 ± 0.364	215.100 ± 1.229
	T	191.039 ± 1.244	156.291 ± 0.980	55.659 ± 0.372	432.902 ± 0.718	108.298 ± 1.335	213.310 ± 0.990
	%	-1.04	-8.87 *	-2.99 *	-0.05	-8.51 *	-0.83
3 weeks	C	192.326 ± 0.203	173.444 ± 1.705	57.287 ± 0.176	430.635 ± 0.928	117.401 ± 0.079	216.757 ± 0.943
	T	183.289 ± 0.903	158.810 ± 0.667	54.040 ± 0.731	434.667 ± 0.745	108.355 ± 0.832	204.485 ± 0.965
	%	-4.70 *	-8.44 *	-5.67 *	0.94 *	-7.70 *	-5.66 *
4 weeks	C	192.276 ± 0.075	173.669 ± 1.772	57.771 ± 0.023	430.951 ± 0.267	118.248 ± 0.380	215.868 ± 1.275
	T	106.746 ± 0.802	146.438 ± 0.901	39.991 ± 0.564	384.944 ± 1.555	92.118 ± 0.763	188.476 ± 1.277
	%	-44.48 *	-15.68 *	-30.78 *	-10.68 *	-22.10 *	-12.69 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t'* test.
% : Percentage of change from control. *: Significant at p<0.05.

Table (4): Effect of chronic oral administration of the benzyl acetate (230 mg/ kg b.w) on gama-aminobutyric acid (GABA) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean ± S.E.	Striatum mean ± S.E.	Cerebral cortex mean ± S.E.	Hypothalamus mean ± S.E.	Brain stem mean ± S.E.	Hippocampus mean ± S.E.
1 week	C	192.457 ± 0.799	171.652 ± 0.450	57.247 ± 0.385	432.828 ± 0.319	118.155 ± 0.197	214.787 ± 1.321
	T	192.417 ± 0.548	171.843 ± 0.986	58.022 ± 0.228	431.512 ± 2.545	116.635 ± 0.890	214.903 ± 0.767
	%	-0.02	0.11	1.35	-0.30	-1.29	0.05
2 weeks	C	192.544 ± 0.759	171.662 ± 0.447	57.374 ± 0.463	432.939 ± 0.370	117.868 ± 0.237	214.933 ± 1.269
	T	138.167 ± 0.477	99.500 ± 0.342	42.667 ± 1.764	255.000 ± 0.856	84.333 ± 0.494	108.833 ± 1.621
	%	-28.24 *	-42.04 *	-25.63 *	-41.10 *	-28.45 *	-49.36 *
3 weeks	C	193.611 ± 0.781	175.423 ± 1.783	57.849 ± 0.675	437.968 ± 1.007	118.436 ± 0.231	216.865 ± 0.870
	T	144.167 ± 1.078	92.000 ± 1.065	40.333 ± 0.422	202.167 ± 0.946	72.333 ± 0.882	85.833 ± 0.601
	%	-25.54 *	-47.56 *	-30.28 *	-53.84 *	-38.93 *	-60.42 *
4 weeks	C	193.379 ± 0.440	171.744 ± 1.615	57.713 ± 0.935	437.849 ± 0.198	118.118 ± 1.398	215.234 ± 1.053
	T	141.167 ± 0.654	70.167 ± 12.440	34.333 ± 0.494	191.333 ± 0.803	65.167 ± 0.477	65.167 ± 0.703
	%	-27.00 *	-59.14 *	-40.51 *	-56.30 *	-44.83 *	-69.72 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t* 'test.
% : Percentage of change from control. *: Significant at p<0.05.

4. Discussion:

The present study provides evidence that artificial strawberry flavour (benzyl Acetate), a widely used flavouring agent in human diet. The present results demonstrated that after the daily oral administration of benzyl acetate NE, DA, 5-HT and GABA contents in all examined regions were reduced in the 2nd week.

In the body, benzyl acetate was hydrolyzed to benzyl acetate, then lyoxidized to benzoicacid Metabolization of benzoate. In the liver the benzoate is combined with glycine[14] and cross the blood-brain barrier. These components are toxic and affect the central nervous system[15] that lead to neurological and behavioural changes such as headaches and insomnia. In addition, these components may changes in brain the content catecholamines which consider important neurotransmitters regulating life-sustaining functions [16-17].

The most important neurotransmitter which has function in interneurons is glycine. Glycine serves as a coagonist for the NMDA receptor because the activation of this receptor requires the binding of glycine [18]. Therefore, glycine binding site on the NMDA receptor is pharmacologically different and distinct from the inhibitory glycine receptor, which can be activated by serine and alanine (different small analogs of glycine). This allows the influx of C1- ions through the neuronal membrane. As a result, this reaction increases the firing threshold and creates an inhibitory action. Then, glycine works as an inhibitory neurotransmitter of neuronal firing through gating C1-channels on this inhibitory process.

Prolonged hyperpolarization of the neuronal membrane and neuronal degeneration.

However, benzyl acetate has ability to stimulate excitatory receptors like the glutamate receptor, the kainic acid receptor, and the N-methyl-D-aspartate. When benzyl acetate combined with glycine will cause blocking of hyperpolarization process. Because the combination depletion the typical glycine then increased excitability of some of neurons and the induction of seizures prolonged hyperpolarization of the neuronal membrane and neuronal degeneration. However, benzyl acetate has ability to stimulate excitatory receptors like the glutamate receptor, the kainic acid receptor, and the N-methyl-D-aspartate. When benzyl acetate combined with glycine will cause blocking of hyperpolarization process. Because the combination depletion the typical glycine then increased excitability of some populations of neurons and the induction of seizures.

Study subjects and animals exposed to benzyl acetate and supplemented with Lalanine have showed increased sensitivity which could explain by NMDA receptor site modulation. Normally, glycine participates in many metabolic reactions and is abundantly available in most tissues of the body. Certain unique chemical structures are able to severely deplete the available reserve of glycine such as benzyl acetate. This makes it possible to study the potential effect of neurodegeneration by glycine [4].

Low glycine levels in the body can cause depletion in glutamine. The primary neurotransmitters: glutamate and GABA are derived from Astrocytic-derived glutamine [19-20].

which have roles in neurotransmission, [21] and play key role functions in the neuronal cycles of the brain, which are involved in motor activities. The sodium benzoate can induce changes in the brain that significantly reduce the zinc level in the brain. This will eventually lead to behavioral changes in the mice[22] Zinc deficiency has also been associated motor function impairment, depression, anxiety, and ADHD symptoms. [23-24-25-26-27].

The sodium benzoate might be changes in the neurotransmitter levels and decrease the gamma-amino butyric acid levels and reduce the level of zinc in the brain. benzyl acetate neurotoxicity induce side effects in the nervous tissue like cerebellum by increasing oxidative stress[28]. The motor impairment of the benzyl acetate treated rats might also be related to inattentive behavior. However, different mechanisms can be considered by which benzyl acetate can influence motor impairment. Metabolization of benzoate in the liver is performed by conjugation with glycine. Yet, reduced of the glycine content in the body caused by using glycine in detoxification of benzoate, which can affect the metabolic process where glycine is included. It has also been reported that a decrease of glycine leads to anxiety [29-30]. Moreover, low glycine levels in the body can cause depletion in glutamine. Beside to their functions in neurotransmission, these neurotransmitters have ability to allow metabolic coupling between astrocytes and neurons. These 2 neurotransmitters (glutamate and GABA) play key role functions in the neuronal cycles of the brain, which are involved in motor activities and therefore the rotarod performance[31].

5. Conclusions:

The impact of benzyl acetate induced significant reduction in brain neurotransmitters Conclusion In Saudi Arabia, benzyl acetate a wide variety of food flavour is used commonly in such products as cakes, soft drinks, fast food and candy. especially In food the school level Saudi Arabia, only some of the approved additives are especially at, to make the public aware of the effect of benzyl acetate on the histology of brain area confirmed the impairment in the motor function of the rats is only speculative but warrants further examination.

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